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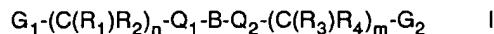
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(54) Diacid-substituted heteroaryl derivatives as matrix metalloproteinase inhibitors

(57) The invention provides dicarboxylic acid-substituted heteroaryl derivatives of the formula



MMP-13. This invention also provides pharmaceutical compositions and methods of treating diseases mediated by MMP-13, including arthritis, asthma, heart disease, atherosclerosis, and osteoporosis, or a pharmaceutically acceptable salt thereof.

or a pharmaceutically acceptable salt thereof, wherein G_1 , G_2 , R_1 , R_2 , R_3 , R_4 , n , m , Q_1 , Q_2 , and B are as defined in the specification. The invention compounds are inhibitors of matrix metalloproteinase enzymes, including

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Description

CROSS-REFERENCE TO RELATED APPLICATIONS

5 [0001] Not applicable

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

10 [0002] Not applicable

10 Reference to a "Microfiche Appendix"

15 [0003] Not applicable

15 BACKGROUND OF THE INVENTION

(1) Field of the Invention

20 [0004] The present invention relates to inhibitors of the enzyme matrix metalloproteinase-13 ("MMP-13"), pharmaceutical compositions comprising said inhibitors, and methods of treating diseases responsive to inhibition of MMP-13 comprising administering said inhibitors. The preceding statement is meant to be illustrative of the field of the invention only, and should not be construed to limit the scope of the present invention, which is fully, clearly, concisely, and exactly described below.

25 (2) Description of the Related Art

30 [0005] Matrix metalloproteinases (sometimes referred to as "MMPs") are naturally-occurring (i.e., endogenous) enzymes found in most mammals. Over-expression and activation of MMPs or an imbalance between MMPs and natural endogenous tissue inhibitors of MMPs (sometimes referred to as "TIMPs") have been suggested as factors in the pathogenesis of diseases characterized by the breakdown of extracellular matrix or connective tissues.

35 [0006] Stromelysin-1 and gelatinase A are members of the matrix metalloproteinase ("MMP") family. Other members of the MMP family include fibroblast collagenase ("MMP-1"), neutrophil collagenase ("MMP-8"), gelatinase B ("92 kDa gelatinase" or "MMP-9"), stromelysin-2 ("MMP-10"), stromelysin-3 ("MMP-11"), matrilysin ("MMP-7"), collagenase-3 ("MMP-13"), and other newly discovered membrane-associated matrix metalloproteinases (Sato H., Takino T., Okada Y., Cao J., Shinagawa A., Yamamoto E., and Seiki M., *Nature*, 1994;370:61-65). Overactivity of these enzymes has been implicated in a number of diseases which result from breakdown of connective tissue or extracellular matrix, including such diseases as rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, multiple sclerosis, gingivitis, corneal epidermal and gastric ulceration, atherosclerosis, neointimal proliferation which leads to restenosis and ischemic heart failure, stroke, renal disease, macular degeneration, and tumor metastasis. Inhibition of MMPs is now a recognized method for preventing and treating these diseases and other diseases responsive to inhibition of MMPs, as MMP inhibitors curtail and/or eliminate the breakdown of connective tissues or extracellular matrices that is intrinsic to these disease states.

40 [0007] MMPs contain a catalytic zinc cation that typically must coordinate to a functional group in a substrate before cleavage of the substrate by the MMP can occur. This catalytic zinc is usually the focal point for inhibitor design. For example, the modification of substrate mimics by introducing zinc-chelating groups has generated potent inhibitors such as peptide hydroxamates and thiol-containing peptides. Peptide hydroxamates and TIMPs have been used successfully to treat animal models of cancer and inflammation. MMP inhibitors have also been used to prevent and treat congestive heart failure and other cardiovascular diseases, as described in United States Patent No. 5,948,780.

45 [0008] A major limitation on the use of currently known MMP inhibitors is their lack of specificity for any particular MMP enzyme. Further, recent studies have shown that MMP inhibitors also inhibit the production of tumor necrosis factor alpha ("TNF- α ") by inhibiting TNF- α converting enzyme ("TACE"), which is also known as TNF- α convertase. Recent data has established that specific MMP enzymes are associated with some diseases, but are not associated with others. A nonselective inhibitor of MMPs may potentially inhibit MMPs that are not involved in the process of the particular disease being treated, thereby "diluting" the inhibitor's effectiveness and, further, possibly leading to undesirable side effects *in vivo*.

55 [0009] The MMPs are generally categorized based on their substrate specificity, and indeed the collagenase subfamily of MMP-1, MMP-8, and MMP-13 preferentially cleave native interstitial collagens, and thus usually are associated only with diseases linked to such interstitial collagen tissue. Nevertheless, it seems some diseases may involve over-

activity of only one MMP. This is indicated by the recent discovery that MMP-13 alone is over expressed in breast carcinoma, while MMP-1 alone is over expressed in papillary carcinoma (see Chen et al., *J. Am. Chem. Soc.*, 2000; 122:9648-9654).

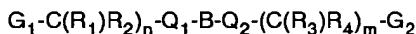
[0010] A selective inhibitor of MMP-13 would thus be valuable. However, there appears to be only one highly selective inhibitor of MMP-13, namely WAY-170523 reported by Chen et al., Supra., 2000. The need continues to find new low molecular weight compounds that are potent and selective MMP inhibitors, and that have an acceptable therapeutic index of toxicity/potency, which makes them amenable for use clinically in the prevention and treatment of the associated disease states.

[0011] One aspect of the present invention is a group of MMP-13 inhibitor compounds characterized as being diacid-substituted heteroaryl derivatives. A further aspect of this invention is MMP-13 inhibitor compounds that are selective inhibitors of MMP-13. All that is needed to practice the invention is to administer from 1 to 6 times daily to a patient in need of treatment, a therapeutically effective amount of a compound of the invention. Determination of dosage forms, amounts of a compound to administer, routes of administration, and identification of patients in need of treatment is discussed below and is within the average skill in veterinary or medical arts.

[0012] The preceding description is for background purposes only, and is not to be construed, in part or in whole, as an admission of prior art.

BRIEF SUMMARY OF THE INVENTION

[0013] This invention provides diacid-substituted heteroaryl derivatives that are inhibitors of matrix metalloproteinase-13 enzymes. The invention is more particularly directed to a compound of Formula I



25 or a pharmaceutically acceptable salt thereof,
wherein:

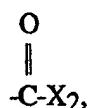
30 G_1 and G_2 are independently selected from:

35 hydrogen,
 C₁-C₁₂ alkyl,
 substituted C₁-C₁₂ alkyl,
 C₂-C₁₂ alkenyl,
 substituted C₂-C₁₂ alkenyl,
 C₂-C₁₂ alkynyl,
 substituted C₂-C₁₂ alkynyl,
 C₃-C₁₂ cycloalkyl,
 substituted C₃-C₁₂ cycloalkyl,
40 phenyl,
 substituted phenyl,
 naphthyl,
 substituted naphthyl,
 heteroaryl, and
45 substituted heteroaryl;

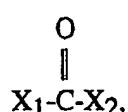
R₁, R₂, R₃, and R₄ are independently, at each occurrence, selected from:

50 hydrogen,
 methyl,
 cyano, and
 fluoro, or R₁ and R₂, or R₃ and R₄ may be taken together with the carbon atom to which they are each attached to form C=O;

55 n and m are independently an integer of from 1 to 3;
 Q₁ is

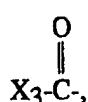


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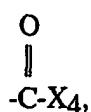


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wherein X_1 and X_2 are independently O or N(H);
 Q_2 is

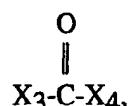


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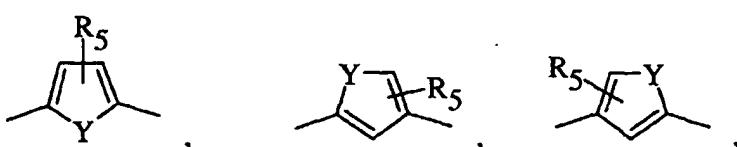
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, or



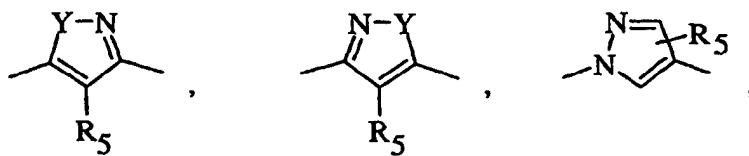
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wherein X_3 and X_4 are independently O or N(H); and
 B is a 5-membered heterocyclene selected from:

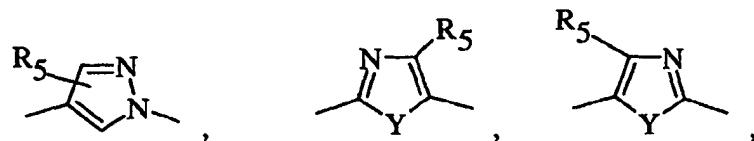


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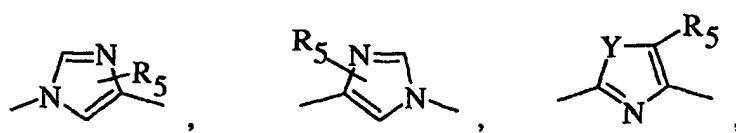


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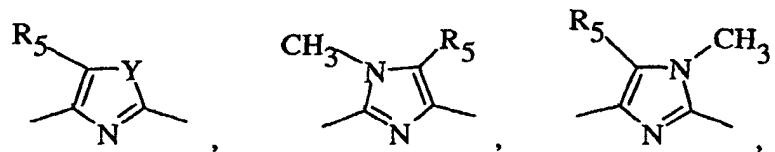


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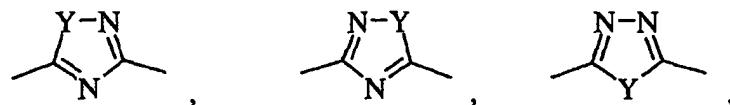
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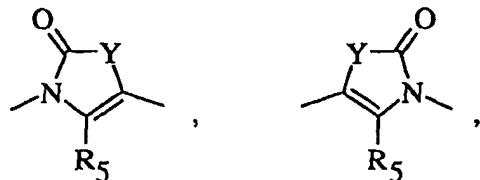


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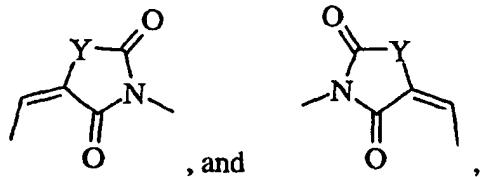
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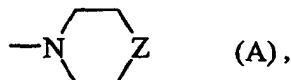


wherein Y is O, S, or N-CH₃; and
 R₅ is selected from:

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hydrogen,
 C₁-C₁₂ alkyl,
 substituted C₁-C₁₂ alkyl,

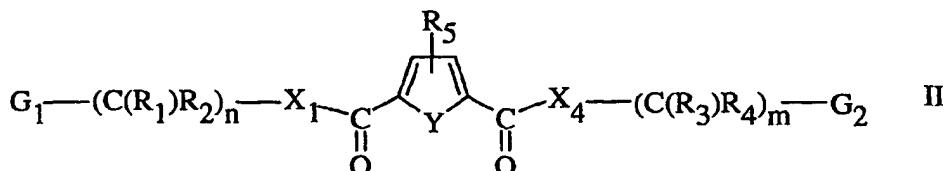
5 C_2 - C_{12} alkenyl,
 substituted C_2 - C_{12} alkenyl,
 C_2 - C_{12} alkynyl,
 substituted C_2 - C_{12} alkynyl,
 10 C_3 - C_{12} cycloalkyl,
 substituted C_3 - C_{12} cycloalkyl,
 phenyl,
 substituted phenyl,
 benzyl,
 15 substituted benzyl,
 $O-R_6$, wherein R_6 is hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl,
 $S-R_6$, wherein R_6 is hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl,
 $C(O)-R_6$, wherein R_6 is hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl,
 CO_2R_6 , wherein R_6 is hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl,
 20 $C(O)-N(H)OR_6$, wherein R_6 is hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl,
 $C(=NOR_6)-H$, wherein R_6 is hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl,
 $C(=NOR_6)-CH_3$, wherein R_6 is hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl,
 CH_2OR_6 , wherein R_6 is hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl,
 $CH_2N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7
 25 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A)



30 wherein Z is CH_2 , O , S , or $N-R$, wherein R is H or CH_3 ,
 $C(H)F-OH$,
 CF_2-OH ,
 $O-C(O)-R_6$, wherein R_6 is hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl,
 $C(O)-N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7
 35 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,
 $N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,
 40 $N(R_6)-C(O)-R_7$, wherein R_6 and R_7 are independently hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl,
 $N(H)-C(O)-N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,
 45 $N(H)-C(O)-OR_6$, wherein R_6 is independently hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl,
 $N(H)-S(O)_2-(C_1-C_{12}$ alkyl),
 $O-C(O)-N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,
 NO_2 ,
 N_3 ,
 50 $N(H)-C(NR_8)-N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1 - C_4 alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above, and R_8 is hydrogen, hydroxy, methoxy, or CN ,
 CN ,

halo,
 S(O)-(C₁-C₁₂ alkyl),
 S(O)₂(C₁-C₁₂ alkyl),
 S(O)₂-N(R₆)-(R₇), wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above, and
 S(O)₂CF₃, wherein at least one of R₁, R₂, R₃, R₄, or R₅ is not hydrogen, or at least one of G₁ or G₂ is substituted C₁-C₁₂ alkyl, substituted C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkynyl, substituted C₃-C₁₂ cycloalkyl, substituted phenyl, substituted naphthyl, or substituted heteroaryl.

[0014] A preferred embodiment of the present invention is a compound of Formula II



or a pharmaceutically acceptable salt thereof, wherein Y is O, S, or N-CH₃, and G₁, G₂, R₁, R₂, R₃, R₄, n, m, X₁, X₄, and R₅ are as defined above for Formula I.

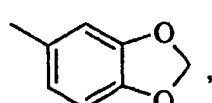
[0015] More preferred is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein Y is S and G₁, G₂, R₁, R₂, R₃, R₄, n, m, X₁, X₄, and R₅ are as defined above for Formula I.

[0016] Still more preferred is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein Y is S, G₁ and G₂ are independently phenyl or substituted phenyl, and R₁, R₂, R₃, R₄, n, m, X₁, X₄, and R₅ are as defined above for Formula I.

[0017] Still more preferred is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein Y is S, G₁ and G₂ are independently substituted phenyl, n and m are each 1, and R₁, R₂, R₃, R₄, X₁, X₄, and R₅ and are as defined above for Formula I.

[0018] Still more preferred is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein Y is S, G₁ and G₂ are independently substituted phenyl, wherein the substituents are selected from 1,2-methylenedioxy, methoxy, ethoxy, -O-C(O)CH₃, carboxy, carbomethoxy, and carboethoxy, n and m are each 1, and R₁, R₂, R₃, R₄, X₁, X₄, and R₅ are as defined above for Formula I.

[0019] Still more preferred is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein Y is S, n and m are each 1, G₁ and G₂ are each



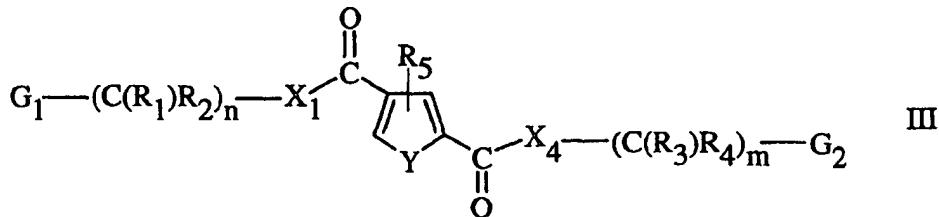
45 R₅ is hydrogen or OMe, and R₁, R₂, R₃, R₄, X₁, and X₄ are as defined above for Formula I.

[0020] Still more preferred is a compound of Formula II, or a pharmaceutically acceptable salt thereof, selected from:

50 thiophene-2,5-dicarboxylic acid, bis[(1,3-benzodioxol-5-ylmethyl) ester];
 thiophene-2,5-dicarboxylic acid, bis[(1,3-benzodioxol-5-ylmethyl) amide];
 thiophene-2,5-dicarboxylic acid, 3-methoxy-, bis[(1,3-benzodioxol-5-ylmethyl) ester]; and
 thiophene-2,5-dicarboxylic acid, 3-methoxy-, bis[(1,3-benzodioxol-5-ylmethyl) amide].

[0021] Also still more preferred is a compound of Formula II, or a pharmaceutically acceptable salt thereof, named 55 3-methoxy-thiophene-2,5-dicarboxylic acid bis-benzylamide.

[0022] Another preferred embodiment of the present invention is a compound of Formula III



10

or a pharmaceutically acceptable salt thereof, wherein Y is O, S, or N-CH₃, and G₁, G₂, R₁, R₂, R₃, R₄, n, m, X₁, X₄, and R₅ are as defined above for Formula I.

15 [0023] More preferred is a compound of Formula III, or a pharmaceutically acceptable salt thereof, wherein Y is S or N-CH₃, and G₁, G₂, R₁, R₂, R₃, R₄, n, m, X₁, X₄, and R₅ are as defined above for Formula I.

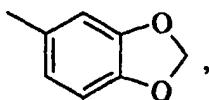
20 [0024] Still more preferred is a compound of Formula III, or a pharmaceutically acceptable salt thereof, wherein Y is S, G₁ and G₂ are independently phenyl or substituted phenyl, and R₁, R₂, R₃, R₄, R₅, n, m, X₁, and X₄ are as defined above for Formula I.

25 [0025] Still more preferred is a compound of Formula III, or a pharmaceutically acceptable salt thereof, wherein Y is S or N-CH₃, G₁ and G₂ are independently substituted phenyl, n and m are each 1, and R₁, R₂, R₃, R₄, X₁, X₄, and R₅ are as defined above for Formula I.

30 [0026] Still more preferred is a compound of Formula III, or a pharmaceutically acceptable salt thereof, wherein Y is S or N-CH₃, G₁ and G₂ are independently substituted phenyl, wherein the substituents are selected from 1,2-methylenedioxy, methoxy, ethoxy, -O-C(O)CH₃, carboxy, carbomethoxy, and carboethoxy, n and m are each 1, and R₁, R₂, R₃, R₄, X₁, X₄, and R₅ are as defined above for Formula I.

35 [0027] Still more preferred is a compound of Formula III, or a pharmaceutically acceptable salt thereof, wherein Y is S, G₁, and G₂ are each

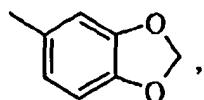
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40 n and m are each 1, and R₁, R₂, R₃, R₄, R₅, X₁, and X₄ are as defined above for Formula I.

45 [0028] Also still more preferred is a compound of Formula III, or a pharmaceutically acceptable salt thereof, wherein Y is N-CH₃, G₁ and G₂ are each

40



50 n and m are each 1, and R₁, R₂, R₃, R₄, R₅, X₁, and X₄ are as defined above for Formula I.

[0029] Still more preferred is a compound of Formula III, or a pharmaceutically acceptable salt thereof, selected from:

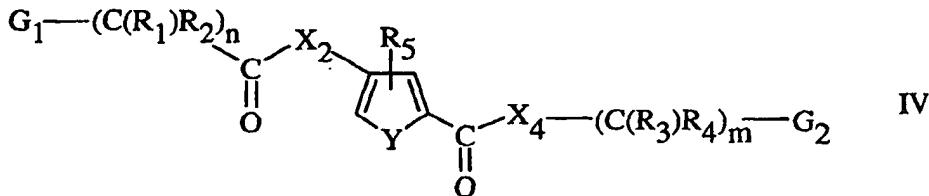
thiophene-2,4-dicarboxylic acid, bis[(1,3-benzodioxol-5-ylmethyl) ester];

thiophene-2,4-dicarboxylic acid, bis[(1,3-benzodioxol-5-ylmethyl) amide];

55 1*H*-pyrrole-2,4-dicarboxylic acid, 1-methyl-, bis[(1,3-benzodioxol-5-ylmethyl) ester]; and
1*H*-pyrrole-2,4-dicarboxylic acid, 1-methyl-, bis[(1,3-benzodioxol-5-ylmethyl) amide].

[0030] Also still more preferred is a compound of Formula III, or a pharmaceutically acceptable salt thereof, named 4-({[5-(4-methoxy-benzylcarbamoyl)-2-methylamino-thiophene-3-carbonyl]-amino}-methyl)-2-methyl-benzoic acid.

[0031] Another preferred embodiment of the present invention is a compound of Formula IV



10 or a pharmaceutically acceptable salt thereof, wherein Y is O, S, or N-CH₃, and G₁, G₂, R₁, R₂, R₃, R₄, n, m, X₂, X₄, and R₅ are as defined above for Formula I.

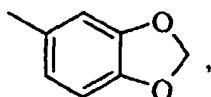
[0032] More preferred is a compound of Formula IV, or a pharmaceutically acceptable salt thereof, wherein Y is S and G₁, G₂, R₁, R₂, R₃, R₄, n, m, X₂, X₄, and R₅ are as defined above for Formula I.

15 [0033] Still more preferred is a compound of Formula IV, or a pharmaceutically acceptable salt thereof, wherein Y is S, G₁ and G₂ are independently phenyl or substituted phenyl, and R₁, R₂, R₃, R₄, R₅, n, m, X₂, and X₄ are as defined above for Formula I.

[0034] Still more preferred is a compound of Formula IV, or a pharmaceutically acceptable salt thereof, wherein Y is S, G₁ and G₂ are independently phenyl or substituted phenyl, n and m are each 1, R₅ is methyl, and R₁, R₂, R₃, R₄, X₂, and X₄ are as defined above for Formula I.

20 [0035] Still more preferred is a compound of Formula IV, or a pharmaceutically acceptable salt thereof, wherein Y is S, G₁ and G₂ are independently phenyl or substituted phenyl, wherein the substituents are selected from 1,2-methylenedioxy, methoxy, ethoxy, -O-C(O)CH₃, carboxy, carbomethoxy, and carboethoxy, n and m are each 1, and R₁, R₂, R₃, R₄, X₂, X₄, and R₅ are as defined above for Formula I.

[0036] Still more preferred is a compound of Formula IV, or a pharmaceutically acceptable salt thereof, wherein Y is 25 S, G₁ is phenyl or substituted phenyl, n and m are each 1, R₅ is methyl, G₂ is

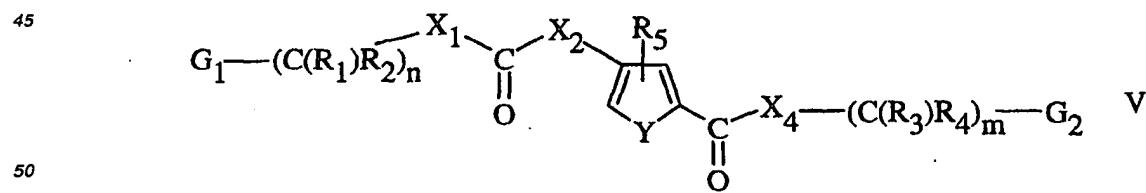


and R₁, R₂, R₃, R₄, X₂, and X₄ are as defined above for Formula I.

[0037] Still more preferred is a compound of Formula IV, or a pharmaceutically acceptable salt thereof, selected from:

thiophene-2-carboxylic acid, 5-methyl-4-phenylacetylaminoo-, benzyl ester;
 thiophene-2-carboxylic acid, 5-methyl-4-phenylacetylaminoo-, benzyl amide;
 thiophene-2-carboxylic acid, 5-methyl-4-phenylacetylaminoo-, 1,3-benzodioxol-5-ylmethyl ester; and
 40 thiophene-2-carboxylic acid, 5-methyl-4-phenylacetylaminoo-, 1,3-benzodioxol-5-ylmethyl amide.

[0038] Another preferred embodiment of the present invention is a compound of Formula V



or a pharmaceutically acceptable salt thereof, wherein Y is O, S, or N-CH₃, and G₁, G₂, R₁, R₂, R₃, R₄, n, m, X₁, X₂, X₄, and R₅ are as defined above for Formula I.

[0039] More preferred is a compound of Formula V, or a pharmaceutically acceptable salt thereof, wherein Y is S, and G₁, G₂, R₁, R₂, R₃, R₄, n, m, X₁, X₂, X₄, and R₅ are as defined above for Formula I.

[0040] Still more preferred is a compound of Formula V, or a pharmaceutically acceptable salt thereof, wherein Y is S, G₁ is phenyl or substituted phenyl, G₂ is phenyl, substituted phenyl, or C₁-C₁₂ alkyl, and R₁, R₂, R₃, R₄, X₁, X₂, X₄,

and R_5 are as defined above for Formula I.

[0041] Still more preferred is a compound of Formula V, or a pharmaceutically acceptable salt thereof, wherein Y is S, G_1 is phenyl or substituted phenyl, G_2 is phenyl, substituted phenyl, or C_1 - C_{12} alkyl, n and m are each 1, and R_1 , R_2 , R_3 , R_4 , X_1 , X_2 , X_4 , and R_5 are as defined above for Formula I.

[0042] Still more preferred is a compound of Formula V, or a pharmaceutically acceptable salt thereof, wherein Y is S, G_1 is phenyl or substituted phenyl, wherein the substituents are selected from 1,2-methylenedioxy, methoxy, ethoxy, -O-C(O)CH₃, carboxy, carbomethoxy, and carboethoxy, G_2 is phenyl, substituted phenyl, wherein the substituents are selected from 1,2-methylenedioxy, methoxy, ethoxy, -O-C(O)CH₃, carboxy, carbomethoxy, and carboethoxy, or C_1 - C_{12} alkyl, n and m are each 1, and R_1 , R_2 , R_3 , R_4 , X_1 , X_2 , X_4 , and R_5 are as defined above for Formula I.

[0043] Still more preferred is a compound of Formula V, or a pharmaceutically acceptable salt thereof, wherein Y is S, G_1 is phenyl, G_2 is methyl or

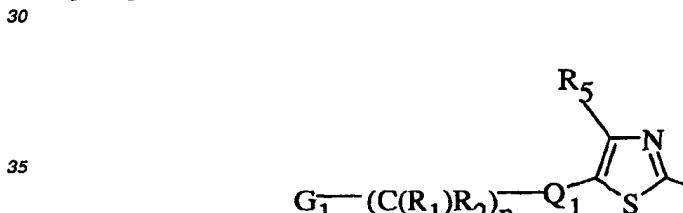


n and m are each 1, R_5 is methyl, and R_1 , R_2 , R_3 , R_4 , X_1 , X_2 , and X_4 are as defined above for Formula I.

[0044] Still more preferred is a compound of Formula V, or a pharmaceutically acceptable salt thereof, selected from:

thiophene-2-carboxylic acid, 4-(3-benzyl-ureido)-5-methyl-, methyl ester;
 thiophene-2-carboxylic acid, 4-(3-benzyl-ureido)-5-methyl-, methyl amide;
 thiophene-2-carboxylic acid, 4-(3-benzyl-ureido)-5-methyl-, benzyl ester;
 thiophene-2-carboxylic acid, 4-(3-benzyl-ureido)-5-methyl-, benzyl amide;
 thiophene-2-carboxylic acid, 4-(3-benzyl-ureido)-5-methyl-, (1,3-benzodioxol-5-ylmethyl) ester; and
 thiophene-2-carboxylic acid, 4-(3-benzyl-ureido)-5-methyl-, (1,3-benzodioxol-5-ylmethyl) amide.

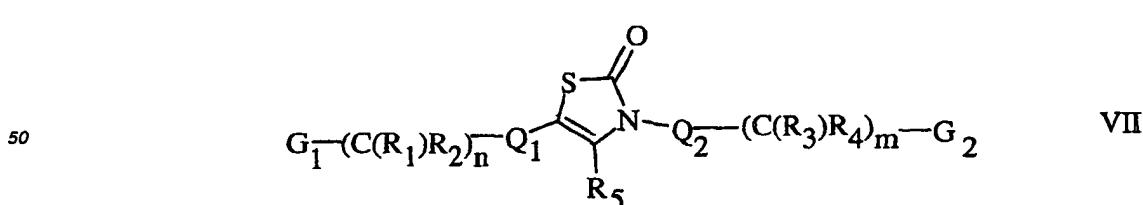
[0045] Another embodiment of the present invention is a compound of Formula VI



or a pharmaceutically acceptable salt thereof, wherein G_1 , G_2 , R_1 , R_2 , R_3 , R_4 , R_5 , n, m, Q_1 , and Q_2 are as defined above for Formula I.

[0046] Another embodiment of the present invention is a compound of Formula VI, or a pharmaceutically acceptable salt thereof, which is 3-methoxy-cyclopentanecarboxylic acid 5-(2-naphthalen-2-yl-ethylcarbamoyl)-4-phenylthiazol-2-yl ester.

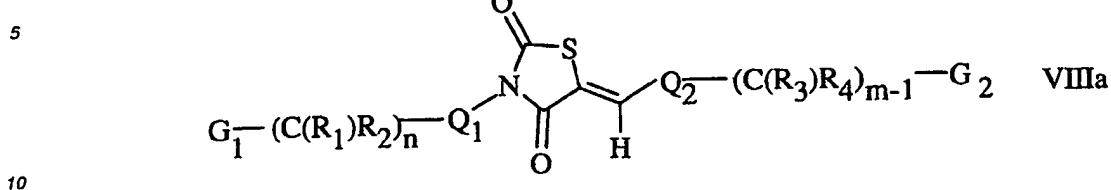
[0047] Another embodiment of the present invention is a compound of Formula VII



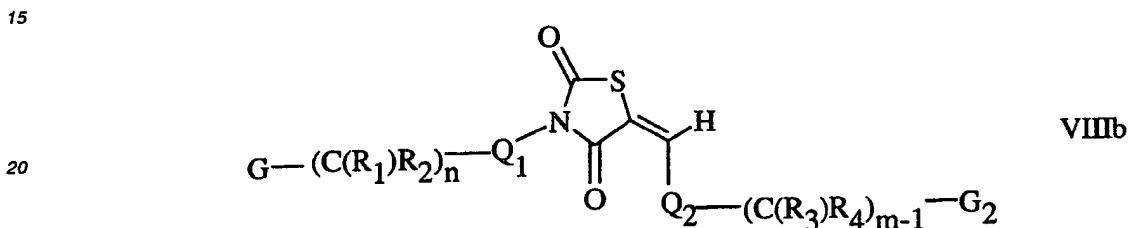
or a pharmaceutically acceptable salt thereof, wherein G_1 , G_2 , R_1 , R_2 , R_3 , R_4 , R_5 , n, m, Q_1 , and Q_2 are as defined above for Formula I.

[0048] Another embodiment of the present invention is a compound of Formula VII, or a pharmaceutically acceptable salt thereof, which is [2-(1H-indol-3-yl)-2-oxo-ethyl]-carbamic acid 3-(3-methyl-but-2-enylcarbamoyl)-2-oxo-2,3-dihydrothiazol-5-yl ester.

[0049] Another embodiment of the present invention is a compound of Formula VIIIa



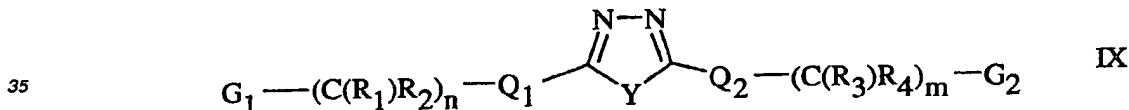
or a pharmaceutically acceptable salt thereof,
or a compound of Formula VIIIb



25 or a pharmaceutically acceptable salt thereof, wherein G₁, G₂, R₁, R₂, R₃, R₄, R₅, n, m, Q₁, and Q₂ are as defined above for Formula I.

[0050] Another embodiment of the present invention is a compound of Formula VIIIa or VIIIb, or a pharmaceutically acceptable salt thereof, which is (Z)-5-(2,2-difluoro-hex-5-ynoyloxymethylene)-2,4-dioxo-thiazolidine-3-carboxylic acid 5-chloro-thiophen-2-ylmethyl ester or (E)-5-(2,2-difluoro-hex-5-ynoyloxymethylene)-2,4-dioxo-thiazolidine-3-carboxylic acid 5-chloro-thiophen-2-ylmethyl ester, respectively.

30 [0051] Another embodiment of the present invention is a compound of Formula IX



or a pharmaceutically acceptable salt thereof, wherein Y, G₁, G₂, R₁, R₂, R₃, R₄, n, m, Q₁, and Q₂ are as defined above for Formula I.

40 [0052] More preferred is a compound of Formula IX, or a pharmaceutically acceptable salt thereof, wherein Y is S and G₁, G₂, R₁, R₂, R₃, R₄, n, m, Q₁, and Q₂ are as defined above for Formula I.

[0053] Still more preferred is a compound of Formula IX, or a pharmaceutically acceptable salt thereof, wherein Y is S and G₁ and G₂ are independently phenyl or substituted phenyl, and R₁, R₂, R₃, R₄, n, m, Q₁, and Q₂ are as defined above for Formula I.

45 [0054] Still more preferred is a compound of Formula IX, or a pharmaceutically acceptable salt thereof, wherein Y is S, G₁ and G₂ independently are phenyl or substituted phenyl, n and m are each 1, and R₁, R₂, R₃, R₄, Q₁, and Q₂ are as defined above for Formula I.

[0055] Still more preferred is a compound of Formula IX named 5-(3-benzylureido)-1,3,4-thiadiazole-2-carboxylic acid benzyl ester, or a pharmaceutically acceptable salt thereof.

50 [0056] A further embodiment of this invention is a pharmaceutical composition, comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable carrier, excipient, or diluent. Preferred compositions comprise a compound of Formulas II, III, IV, V, VI, VII, VIIIa, or VIIIb. Other preferred compositions comprise a compound of Formula IX.

[0057] Another embodiment of this invention is a method of treating a patient that has a disease mediated by MMP-13 and optionally from 0 to 15 additional MMP enzymes, comprising administering to said patient a therapeutically effective amount of a pharmaceutical composition which comprises a compound of Formula I, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable carrier, excipient, or diluent. Preferred methods administer a pharmaceutical composition which comprises a compound of Formulas II, III, IV, V, VI, VII, VIIIa, or VIIIb.

Other preferred methods administer a pharmaceutical composition which comprises a compound of Formula IX.

[0058] Another embodiment of this invention is a method for inhibiting MMP-13, comprising administering to a patient in need thereof an MMP-13 inhibiting amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. Preferred methods administer a compound of Formulas II, III, IV, V, VI, VII, VIIa, or VIIb. Other preferred methods administer a compound of Formula IX.

[0059] Another embodiment of this invention is a method of preventing connective tissue or extracellular matrix degradation mediated by MMP-13 and optionally from 0 to 15 additional MMP enzymes, comprising administering to a patient in need thereof an MMP-13 inhibiting amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. Preferred methods of preventing administer a compound of Formulas II, III, IV, V, VI, VII, VIIa, or VIIb.

5 10 Other preferred methods of preventing administer a compound of Formula IX.

[0060] Preferred is a method of preventing connective tissue or extracellular matrix degradation mediated by MMP-13 and optionally from 0 to 15 additional MMP enzymes, comprising administering to a patient in need thereof an MMP-13 inhibiting amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein the patient being treated is at risk for, or has, a disease selected from: cancer, especially breast carcinoma, inflammation, heart failure, asthma, cancer metastasis, multiple sclerosis, corneal epidermal ulceration, gastric ulceration, stroke, renal disease, macular degeneration, atherosclerosis, neointimal proliferation, osteoporosis, periodontitis, gingivitis, an autoimmune disease, a hyper-immune disease, and arthritis, including osteoarthritis and rheumatoid arthritis.

15 [0061] Another preferred method of preventing according to this invention is prevention of connective tissue or extracellular matrix degradation in a patient at risk for, or has, an autoimmune disease.

20 [0062] Another preferred method of preventing according to this invention is prevention of connective tissue or extracellular matrix degradation in a patient at risk for, or has, a hyper-immune disease.

[0063] Another preferred method of preventing according to this invention is prevention of connective tissue or extracellular matrix degradation in a patient at risk for, or has, cancer.

25 [0064] Another preferred method of preventing according to this invention is prevention of connective tissue or extracellular matrix degradation in a patient at risk for, or has, cancer, which cancer is a breast carcinoma.

[0065] Another preferred method of preventing according to this invention is prevention of connective tissue or extracellular matrix degradation in a patient at risk for, or has, inflammation.

[0066] Another preferred method of preventing according to this invention is prevention of connective tissue or extracellular matrix degradation in a patient at risk for, or has, heart failure.

30 [0067] Another preferred method of preventing according to this invention is prevention of connective tissue or extracellular matrix degradation in a patient at risk for, or has, rheumatoid arthritis.

[0068] Another preferred method of preventing according to this invention is prevention of connective tissue or extracellular matrix degradation in a patient at risk for, or has, osteoarthritis.

35 [0069] Another preferred method of preventing according to this invention is prevention of connective tissue or extracellular matrix degradation in a patient at risk for, or has, asthma.

[0070] Another preferred method of preventing according to this invention is prevention of connective tissue or extracellular matrix degradation in a patient at risk for, or has, osteoporosis.

[0071] Another preferred method of preventing according to this invention is prevention of connective tissue or extracellular matrix degradation in a patient at risk for, or has, multiple sclerosis.

40 [0072] Another preferred method of preventing according to this invention is prevention of connective tissue or extracellular matrix degradation in a patient at risk for, or has, cancer metastasis.

[0073] A further embodiment is a method of treating a patient that has a disease mediated by MMP-13 enzymes and optionally from 0 to 15 additional MMP enzymes, comprising administering to said patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. Preferred methods administer a compound of Formulas II, III, IV, V, VI, VII, VIIa, or VIIb. Other preferred methods administer a compound of Formula IX.

45 [0074] A preferred method of treating according to this invention is treatment of a patient that has a disease selected from cancer, especially breast carcinoma, inflammation, and heart failure. Other preferred methods of treating according to this invention include treatment of a patient that has asthma, cancer metastasis, multiple sclerosis, osteoporosis, an autoimmune disease, a hyper-immune disease, arthritis, including osteoarthritis and rheumatoid arthritis, periodontitis, gingivitis, corneal epidermal ulceration, gastric ulceration, stroke, renal disease, macular degeneration, atherosclerosis, or neointimal proliferation.

50 [0075] Another preferred method of treating according to this invention is treatment of a patient that has an autoimmune disease.

[0076] Another preferred method of treating according to this invention is treatment of a patient that has a hyper-immune disease.

55 [0077] Another preferred method of treating according to this invention is treatment of a patient that has cancer.

[0078] Another preferred method of treating according to this invention is treatment of a patient that has cancer, wherein the cancer is a breast carcinoma.

[0079] Another preferred method of treating according to this invention is treatment of a patient that has inflammation.

[0080] Another preferred method of treating according to this invention is treatment of a patient that has heart failure.

[0081] Another preferred method of treating according to this invention is treatment of a patient that has rheumatoid arthritis.

5 [0082] Another preferred method of treating according to this invention is treatment of a patient that has osteoarthritis.

[0083] Another preferred method of treating according to this invention is treatment of a patient that has asthma.

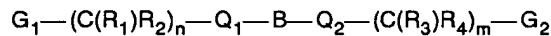
[0084] Another preferred method of treating according to this invention is treatment of a patient that has osteoporosis.

[0085] Another preferred method of treating according to this invention is treatment of a patient that has multiple sclerosis.

10 [0086] Another preferred method of treating according to this invention is treatment of a patient that has cancer metastasis.

[0087] Another embodiment of the present invention is a pharmaceutical composition, comprising a means for inhibiting MMP-13 and a pharmaceutically acceptable carrier, diluent, or excipient.

15 [0088] Still another embodiment of the present invention is an inhibitor of MMP-13, comprising an inhibitor of MMP-13 of Formula I



I

20 or a pharmaceutically acceptable salt thereof,
wherein:

G_1 and G_2 are independently selected from:

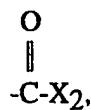
25 hydrogen,
 C_1 - C_{12} alkyl,
 substituted C_1 - C_{12} alkyl,
 C_2 - C_{12} alkenyl,
 substituted C_2 - C_{12} alkenyl,
 30 C_2 - C_{12} alkynyl,
 substituted C_2 - C_{12} alkynyl,
 C_3 - C_{12} cycloalkyl,
 substituted C_3 - C_{12} cycloalkyl,
 phenyl,
 35 substituted phenyl,
 naphthyl,
 substituted naphthyl,
 heteroaryl, and
 substituted heteroaryl;

40 R_1 , R_2 , R_3 , and R_4 are independently, at each occurrence, selected from:

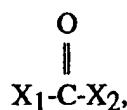
45 hydrogen,
 methyl,
 cyano, and
 fluoro, or R_1 and R_2 , or R_3 and R_4 , may be taken together with the carbon atom to which they are each attached to form $C=O$;

50 n and m are independently an integer of from 1 to 3;
 Q_1 is

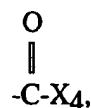
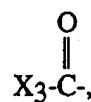




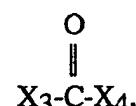
or



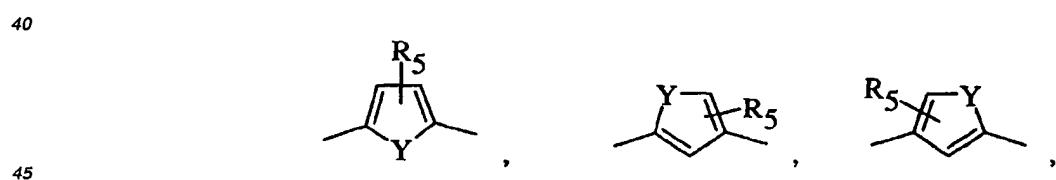
15 wherein X_1 and X_2 are independently O or N(H);
 Q_2 is



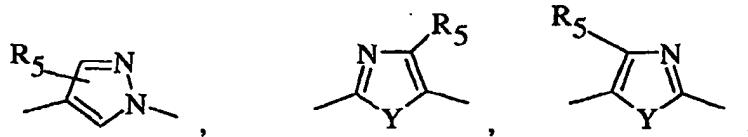
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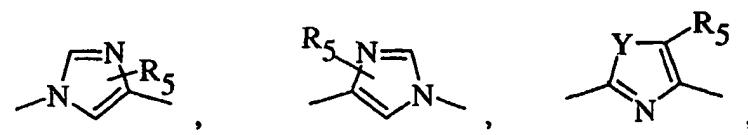
35 wherein X_3 and X_4 are independently O or N(H); and
 B is a 5-membered heterocyclene selected from:



5

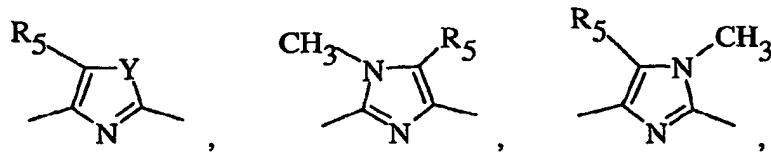


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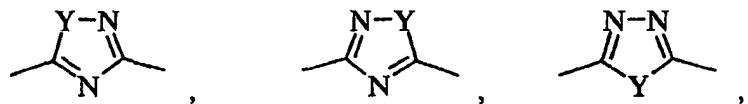


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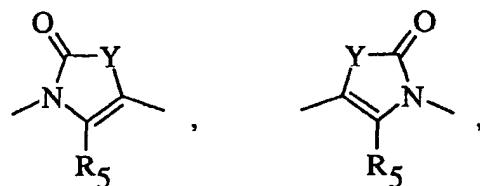


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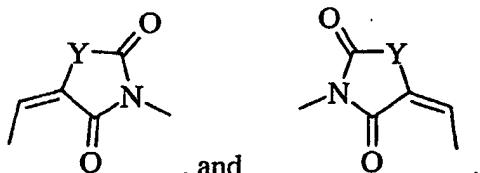
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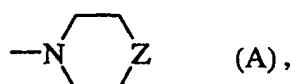
wherein Y is O, S, or N-CH₃, and
R₅ is selected from:

50

hydrogen,
C₁-C₁₂ alkyl,
substituted C₁-C₁₂ alkyl,
C₂-C₁₂ alkenyl,
substituted C₂-C₁₂ alkenyl,
C₂-C₁₂ alkynyl,
substituted C₂-C₁₂ alkynyl,
C₃-C₁₂ cycloalkyl,

substituted C₃-C₁₂ cycloalkyl,
 phenyl,
 substituted phenyl,
 5 benzyl,
 substituted benzyl,
 O-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 S-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 C(O)-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 CO₂R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 10 C(O)-N(H)OR₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 C(=NOR₆)-H, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 C(=NOR₆)-CH₃, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 CH₂OR₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 15 CH₂N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A)

20



25 wherein Z is CH₂, O, S, or N-R, wherein R is H or CH₃,
 C(H)F-OH,
 CF₂-OH,
 O-C(O)-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 30 C(O)-N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,
 N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,
 35 N(R₆)-C(O)-R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 N(H)-C(O)-N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,
 40 N(H)-C(O)-OR₆, wherein R₆ is independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 N(H)-S(O)₂-(C₁-C₁₂ alkyl),
 45 O-C(O)-N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,
 NO₂,
 N₃,
 50 N(H)-C(NR₈)-N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₄ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above, and R₈ is hydrogen, hydroxy, methoxy, or CN,
 CN,
 55 halo,
 S(O)-(C₁-C₁₂ alkyl),
 S(O)₂-(C₁-C₁₂ alkyl),
 S(O)₂-N(R₆)-(R₇), wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and

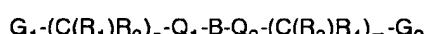
R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above, and

5 $S(O)_2CF_3$, wherein at least one of R_1 , R_2 , R_3 , R_4 , or R_5 is not hydrogen, or at least one of G_1 or G_2 is substituted C_1 - C_{12} alkyl, substituted C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkynyl, substituted C_3 - C_{12} cycloalkyl, substituted phenyl, substituted naphthyl, or substituted heteroaryl.

- [0089] Preferred is the inhibitor of MMP-13 wherein the inhibitor selectively inhibits MMP-13 over RAMP-1.
- [0090] Also preferred is the inhibitor of MMP-13 wherein the inhibitor selectively inhibits RAMP-13 over MMP-2.
- 10 [0091] Also preferred is the inhibitor of MMP-13 wherein the inhibitor selectively inhibits MMP-13 over MMP-3.
- [0092] Also preferred is the inhibitor of MMP-13 wherein the inhibitor selectively inhibits MMP-13 over MMP-7.
- [0093] Also preferred is the inhibitor of MMP-13 wherein the inhibitor selectively inhibits MMP-13 over MMP-8.
- [0094] Also preferred is the inhibitor of MMP-13 wherein the inhibitor selectively inhibits MMP-13 over MMP-9.
- 15 [0095] Also preferred is the inhibitor of MMP-13 wherein the inhibitor selectively inhibits MMP-13 over MMP-10.
- [0096] Also preferred is the inhibitor of MMP-13 wherein the inhibitor selectively inhibits MMP-13 over MMP-11.
- [0097] Also preferred is the inhibitor of MMP-13 wherein the inhibitor selectively inhibits MMP-13 over MMP-12.
- [0098] Also preferred is the inhibitor of MMP-13 wherein the inhibitor selectively inhibits MMP-13 over MMP-14.
- [0099] Also preferred is the inhibitor of MMP-13 wherein the inhibitor selectively inhibits MMP-13 over MMP-15.
- 20 [0100] Also preferred is the inhibitor of MMP-13 wherein the inhibitor selectively inhibits MMP-13 over MMP-16.
- [0101] Also preferred is the inhibitor of MMP-13 wherein the inhibitor selectively inhibits MMP-13 over MMP-17.
- [0102] Also preferred is the inhibitor of MMP-13 wherein the inhibitor selectively inhibits MMP-13 over MMP-18.
- [0103] Also preferred is the inhibitor of MMP-13 wherein the inhibitor selectively inhibits MMP-13 over MMP-19.
- 25 [0104] Also preferred is the inhibitor of MMP-13 wherein the inhibitor selectively inhibits MMP-13 over TNF- α converting enzyme.

DETAILED DESCRIPTION OF THE INVENTION

[0105] This invention provides a compound of Formula I



I

or a pharmaceutically acceptable salt thereof, wherein G_1 , G_2 , R_1 , R_2 , R_3 , R_4 , n , m , Q_1 , Q_2 , and B are as defined above for Formula I.

35 [0106] If $n=m=0$ and G_1 and G_2 are phenyl or substituted phenyl, the compounds are not selective inhibitors of MMP-13, and are not part of the instant invention compounds.

[0107] As used herein, the term " C_1 - C_{12} alkyl" means a straight or branched, unsubstituted hydrocarbon group having from 1 to 12 carbon atoms. Preferred C_1 - C_{12} alkyl groups are C_1 - C_6 alkyl. Typical examples of C_1 - C_{12} alkyl groups include methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, and 40 1-hexyl, which are all also C_1 - C_6 alkyl groups, and 1-heptyl, 4-heptyl, 2-octyl, 2-methyl-hept-2-yl, 1-nonyl, 1-decyl, 1-undecyl, 1-dodecyl, 2-dodecyl, 2,4-dimethyl-2-decyl, and 2-(1-methylethyl)-1-nonyl.

[0108] The phrase "substituted C_1 - C_{12} alkyl" means a straight or branched, hydrocarbon group having from 1 to 12 carbon atoms, which is substituted with from 1 to 4 substituents as described below. Illustrative examples of substituted C_1 - C_{12} alkyl are provided below.

45 [0109] The term " C_1 - C_4 alkyl" means a straight or branched unsubstituted hydrocarbon group having from 1 to 4 carbon atoms. Illustrative C_1 - C_4 alkyl groups include methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, and 1,1-dimethylethyl.

[0110] The term " C_2 - C_{12} alkenyl" means a straight or branched, unsubstituted hydrocarbon group having from 2 to 50 12 carbon atoms and 1 or 2 sites of unsaturation (i.e., 1 or 2 $C=C$ bonds). Preferred C_2 - C_{12} alkenyl groups are C_2 - C_6 alkenyl. Typical examples of C_2 - C_{12} alkenyl groups include ethenyl, 1-propen-1-yl, 1-propen-2-yl, 2-propen-1-yl, 1-buten-3-yl, 2-penten-2-yl, and 1-hexen-6-yl, which are all also C_2 - C_6 alkenyl groups, and 1-hepten-3-yl, 3-hepten-1-yl, 2-octen-6-yl, 2-methyl-hept-2-en-4-yl, 1-nonen-8-yl, 1-decen-1-yl, 1-undecen-5-yl, and 2,4-dimethyl-2-decen-1-yl.

[0111] The phrase "substituted C_2 - C_{12} alkenyl" means a straight or branched, hydrocarbon group having from 2 to 55 12 carbon atoms, and 1 or 2 sites of unsaturation (i.e., 1 or 2 $C=C$ bonds), which is substituted with from 1 to 4 substituents as described below. Illustrative examples of substituted C_2 - C_{12} alkenyl are provided below.

[0112] The term " C_2 - C_{12} alkynyl" means a straight or branched, unsubstituted hydrocarbon group having from 2 to 12 carbon atoms and 1 or 2 sites of double unsaturation (i.e., 1 or 2 $C\equiv C$ bonds). Preferred C_2 - C_{12} alkynyl groups are

C_2 - C_6 alkynyl. Typical examples of C_2 - C_{12} alkynyl groups include ethenyl, 1-propyn-1-yl, 1-propyn-3-yl, 1-butyn-3-yl, 2-pentyn-1-yl, and 1-hexyn-6-yl, which are all also C_2 - C_6 alkynyl groups, and 1-heptyn-3-yl, 3-heptyn-1-yl, 2-octyn-6-yl, 2-methyl-hept-3-yn-5-yl, 1-nonyn-8-yl, 1-decyn-1-yl, 1-undecyn-5-yl, and 2,4-dimethyl-5-decyn-1-yl.

[0113] The phrase "substituted C_2 - C_{12} alkynyl" means a straight or branched, hydrocarbon group having from 2 to 12 carbon atoms, and 1 or 2 sites of unsaturation (i.e., 1 or 2 $C\equiv C$ bonds), which is substituted with from 1 to 4 substituents as described below. Illustrative examples of substituted C_2 - C_{12} alkynyl are provided below.

[0114] The term " C_3 - C_6 cycloalkyl" means an unsubstituted cyclic hydrocarbon group having from 3 to 6 carbon atoms. The group C_3 - C_6 cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0115] The term " C_3 - C_{12} cycloalkyl" means an unsubstituted cyclic hydrocarbon group having from 3 to 12 carbon atoms. Preferred C_3 - C_{12} cycloalkyl groups are C_3 - C_6 cycloalkyl. Illustrative examples of C_3 - C_{12} cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, and cyclododecyl.

[0116] The phrase "substituted C_3 - C_{12} cycloalkyl" means a cyclic hydrocarbon group having from 3 to 12 carbon atoms, which is substituted with from 1 to 4 substituents as described below. Illustrative examples of substituted C_3 - C_{12} cycloalkyl are provided below.

[0117] As described above, substituted C_1 - C_{12} alkyl, substituted C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkynyl, and substituted C_3 - C_{12} cycloalkyl are substituted with from 1 to 4 substituents. The substituents are independently selected from:

20 oxo,
 $O-R_z$, wherein R_z is hydrogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, phenyl, or benzyl, wherein phenyl and benzyl may be substituted with from 1 to 3 substituents as described below,

$S-R_z$, wherein R_z is hydrogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, phenyl, or benzyl, wherein phenyl and benzyl may be substituted with from 1 to 4 substituents as described below,

25 $C(O)-R_z$, wherein R_z is hydrogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, phenyl, or benzyl, wherein phenyl and benzyl may be substituted with from 1 to 4 substituents as described below,

CO_2R_z , wherein R_z is hydrogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, phenyl, or benzyl, wherein phenyl and benzyl may be substituted with from 1 to 4 substituents as described below,

30 $C(O)-N(H)OR_z$, wherein R_z is hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl,

$C(=NOR_z)-H$, wherein R_z is hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl,

$C(=NOR_z)-CH_3$, wherein R_z is hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl,

$C(H)F-OH$,

35 $O-C(O)-R_z$, wherein R_z is hydrogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, phenyl, or benzyl, wherein phenyl and benzyl may be substituted with from 1 to 4 substituents as described below,

40 $C(O)-N(R_z)R_y$, wherein R_z and R_y are independently hydrogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, phenyl, or benzyl, wherein phenyl and benzyl may be substituted with from 1 to 4 substituents as described below, or R_z and R_y are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (Z),



45 wherein Y is CH_2 , O , S , or $N-R$, wherein R is H or CH_3 ,

$N(R_z)R_y$, wherein R_z and R_y are independently hydrogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, phenyl, or benzyl, wherein phenyl and benzyl may be substituted with from 1 to 4 substituents as described below, or R_z and R_y are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (Z), wherein (Z) is as defined above,

50 $N(R_z)-C(O)-R_y$, wherein R_z and R_y are independently hydrogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, phenyl, or benzyl, wherein phenyl and benzyl may be substituted with from 1 to 4 substituents as described below,

$N(H)-C(O)-N(R_z)R_y$, wherein R_z and R_y are independently hydrogen, C_1 - C_4 alkyl, phenyl, or benzyl, wherein phenyl and benzyl may be substituted with from 1 to 4 substituents as described below, or R_z and R_y are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1

55 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (Z), wherein (Z) is as defined above,

5 $N(H)-C(O)-OR_z$, wherein R_z is independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, phenyl, or benzyl, wherein phenyl and benzyl may be substituted with from 1 to 4 substituents as described below,
 $O-C(O)-N(R_z)R_y$, wherein R_z and R_y are independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, phenyl, or benzyl, wherein phenyl and benzyl may be substituted with from 1 to 4 substituents as described below, or R_z and R_y are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (Z), wherein (Z) is as defined above,

10 NO_2 ,

11 N_3 ,

12 $N(H)-C(NR_x)-N(R_z)R_y$, wherein R_z and R_y are independently hydrogen, C_1-C_4 alkyl, phenyl, or benzyl, wherein phenyl and benzyl may be substituted with from 1 to 4 substituents as described below, or R_z and R_y are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (Z), wherein (Z) is as defined above, and R_x is hydrogen, hydroxy, methoxy, or CN,

13 CN ,

14 halo,

15 $S(O)-(C_1-C_4$ alkyl),

16 $S(O)_2-(C_1-C_4$ alkyl),

17 $S(O)_2-N(R_z)R_y$, wherein R_z and R_y are independently hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, phenyl, or benzyl, wherein phenyl and benzyl may be substituted with from 1 to 4 substituents as described below, or R_z and R_y are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (Z), wherein (Z) is as defined above, and

18 $N(H)-S(O)_2-(C_1-C_4$ alkyl).

25

[0118] Illustrative examples of substituted C_1-C_{12} alkyl groups include CH_2OH , CF_2OH , $CH_2C(CH_3)_2CO_2CH_3$, CF_3 , $C(O)CF_3$, $C(O)-CH_3$, $(CH_2)_4-S-CH_3$, $CH(CO_2H)CH_2CH_2C(O)NMe_2$, $(CH_2)_5NH-C(O)-NH_2$, $CH_2-CH_2-C(H)-(4\text{-fluorophenyl})$, $CH(OCH_3)CH_2CH_3$, $(CH_2)_9-(\text{morpholin-4-yl})$, $CH_2SO_2NH_2$, and $CH(CH_3)CH_2CH_2OC(O)CH_3$.

26

[0119] Illustrative examples of substituted C_2-C_{12} alkenyl groups include $C(H)=C(H)CH_2OH$, $CH=CF_2$, $CH_2C(H)=C(H)-(CH_2)_2CF_2OH$, $CH_2C(=CH_2)CO_2CH_3$, $C(H)=C(H)-CF_3$, $CH_2-CH_2-C(H)=C(H)-C(O)-CH_3$, $C(H)=C(CH_3)-S-CH_3$, $C(H)=C(H)-C(H)=C(CH_3)-CO_2Me$, $(CH_2)_{12}-CH_2$ -phenyl, and $C(H)=C=C(H)OC(O)CH_3$.

27

[0120] Illustrative examples of substituted C_2-C_{12} alkynyl groups include $C\equiv CCH_2OH$, $C\equiv CF$, $CH_2C\equiv C-(CH_2)_2CF_2OH$, $C\equiv C-CH_2CO_2CH_3$, $CH_2C\equiv C-CF_3$, $CH_2-CH_2-C\equiv C-C(O)-CH_3$, $C\equiv C-S-CH_3$, and $C\equiv C-C(O)OC(O)CH_3$.

28

[0121] Illustrative examples of substituted C_3-C_{12} cycloalkyl groups include 1-hydroxy-cyclopropyl, cyclobutanon-3-yl, 3-(3-phenyl-ureido)-cyclopent-1-yl, 4-carboxy-cyclohexyl, and 9-trifluoromethyl-cyclododecanyl.

29

[0122] The phrase "5-membered heterocyclene" means a 5-membered, monocyclic, aromatic or pseudo aromatic ring diradical, wherein two of the five ring atoms each bear a radical, having carbon atoms, which carbon atoms may be unsubstituted or substituted with oxo or the group R_5 , wherein R_5 is as defined above, and from 1 to 3 heteroatoms selected from N, O, and S, with the provisos that (i) each of the two ring atoms bearing a radical are not directly bonded to each other and (ii) not more than 1 heteroatom atom which is O or S is present.

30

[0123] Illustrative examples of unsubstituted 5-membered heterocyclene include thiophen-2,5-diyl, furan-2,4-diyl, pyrrol-3,5-diyl, pyrrol-1,3-diyl, imidazol-1,4-diyl, isoxazol-3,5-diyl, oxazol-2,4-diyl, thiazol-2,5-diyl, 1,2,4-oxadiazol-3,5-diyl, 1,2,4-triazol-1,3-diyl, and pyrazol-1,3-diyl.

31

[0124] Illustrative examples of substituted 5-membered heterocyclene include 3-methyl-thiophen-2,5-diyl, 3-carbomethoxy-furan-2,4-diyl, 1-benzyl-pyrrol-3,5-diyl, 2-chloro-imidazol-1,4-diyl, 4-cyano-isoxazol-3,5-diyl, 5-methoxy-oxazol-2,4-diyl, 4-acetyl-thiazol-2,5-diyl, and 5-imino-pyrazol-1,3-diyl.

32

[0125] The phrase "substituted phenyl" means phenyl substituted with from 1 to 4 substituents as described below. Illustrative examples of substituted phenyl are provided below.

33

[0126] The phrase "substituted benzyl" means a substituted phenyl, wherein substituted phenyl is as described above, bonded through a CH_2 group. Illustrative examples of substituted benzyl are provided below.

[0127] The term "naphthyl" includes 1-naphthyl and 2-naphthyl.

[0128] The phrase "substituted naphthyl" means substituted 1-naphthyl or substituted 2-naphthyl, each substituted with from 1 to 4 substituents as described below. Illustrative examples of substituted naphthyl are provided below.

34

[0129] The term "heteroaryl" means a 5-membered, monocyclic heteroaryl, a 6-membered, monocyclic heteroaryl, or a 9- or 10-membered, fused-bicyclic heteroaryl, which are as defined below:

(i) The phrase "5-membered, monocyclic heteroaryl" means a 5-membered, monocyclic, aromatic ring group hav-

ing carbon atoms and from 1 to 4 heteroatoms selected from N, O, and S, with the proviso that not more than 1 heteroatom atom which is O or S is present;

(ii) The phrase "6-membered, monocyclic heteroaryl" means a 6-membered, monocyclic, aromatic ring group having carbon atoms and 1 or 2 nitrogen atoms; and

(iii) The phrase "9- or 10-membered, fused-bicyclic heteroaryl" means a 9-membered or 10-membered, aromatic, fused-bicyclic ring group having carbon atoms and from 1 to 4 heteroatoms selected from N, O, and S, with the proviso that not more than 2 heteroatoms which are oxygen atoms and/or sulfur atoms are present, and further that when 2 heteroatoms which are O and/or S are present, the oxygen atoms and/or sulfur atoms are not bonded to each other.

[0130] Illustrative examples of a 5-membered, monocyclic heteroaryl include thiophen-2-yl, furan-2-yl, pyrrol-3-yl, pyrrol-1-yl, imidazol-4-yl, isoxazol-3-yl, oxazol-2-yl, thiazol-4-yl, tetrazol-1-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-triazol-1-yl, and pyrazol-3-yl. Substituted 5-membered, monocyclic heteroaryl is described below.

[0131] Illustrative examples of a 6-membered, monocyclic heteroaryl include pyridin-2-yl, pyridin-4-yl, pyrimidin-2-yl, pyridazin-4-yl, and pyrazin-2-yl. Substituted 6-membered, monocyclic heteroaryl is described below.

[0132] Illustrative examples of a 9- or 10-membered, fused-bicyclic heteroaryl include indol-2-yl, indol-6-yl, iso-indol-2-yl, benzimidazol-2-yl, benzimidazol-1-yl, benztriazol-1-yl, benztriazol-5-yl, quinolin-2-yl, isoquinolin-7-yl, benzopyrimidin-2-yl, benzoxazol-2-yl, benzothiophen-5-yl, and benzofuran-3-yl. Substituted 9- or 10-membered, bicyclic heteroaryl is described below.

[0133] The phrase "substituted heteroaryl" means a substituted 5-membered, monocyclic heteroaryl, a substituted 6-membered, monocyclic heteroaryl, or a substituted 9- or 10-membered, fused-bicyclic heteroaryl, which are as defined below:

(i) The phrase "substituted 5-membered, monocyclic heteroaryl" means a 5-membered, monocyclic, aromatic ring group having carbon atoms and from 1 to 4 heteroatoms selected from N, O, and S, which is substituted with 1 or 2 substituents as defined below, with the proviso that not more than 1 heteroatom atom which is O or S is present, and further that each substituent is not bonded to an oxygen atom or a sulfur atom;

(ii) The phrase "substituted 6-membered, monocyclic heteroaryl" means a 6-membered, monocyclic, aromatic ring group having carbon atoms and 1 or 2 nitrogen atoms, which is substituted with 1 or 2 substituents as defined below, with the proviso that each substituent is not bonded to a nitrogen atom; and

(iii) The phrase "substituted 9- or 10-membered, fused-bicyclic heteroaryl" means a 9-membered or 10-membered, fused-bicyclic, aromatic ring group having carbon atoms and from 1 to 4 heteroatoms selected from N, O, and S, which is substituted with from 1 to 3 substituents as defined below, with the proviso that not more than 2 heteroatoms which are O and/or S are present, and further that when 2 heteroatoms which are O and/or S atoms are present, the O and/or S atoms are not bonded to each other, and further that each substituent is not bonded to an oxygen atom or a sulfur atom.

[0134] Illustrative examples of a substituted, 5-membered, monocyclic heteroaryl, substituted, 6-membered, monocyclic heteroaryl, and substituted 9- or 10-membered, fused-bicyclic heteroaryl are provided below.

[0135] The substituents for substituted phenyl, substituted benzyl, substituted naphthyl (i.e., substituted 1-naphthyl or substituted 2-naphthyl), substituted 5-membered, monocyclic heteroaryl, substituted 6-membered, monocyclic heteroaryl, and substituted 9- or 10-membered, fused-bicyclic heteroaryl are independently selected from:

C₁-C₁₂ alkyl,

C₂-C₁₂ alkenyl,

C₂-C₁₂ alkynyl,

C₃-C₁₂ cycloalkyl,

phenyl,

benzyl,

O-R_z, wherein R_z is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,

S-R_z, wherein R_z is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,

1,2-methylenedioxy,

C(O)-R_z, wherein R_z is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,

CO₂R_z, wherein R_z is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,

C(O)-N(H)OR_z, wherein R_z is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,

C(=NOR_z)-H, wherein R_z is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,

C(=NOR_z)-CH₃, wherein R_z is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,

CH₂OR_z, wherein R_z is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,

CH₂N(R_z)R_y, wherein R_z and R_y are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R_z and R_y are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (Z), wherein (Z) is as defined above,

5 C(H)F-OH,

CF₂-OH,

O-C(O)-R_z, wherein R_z is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,

10 C(O)-N(R_z)R_y, wherein R_z and R_y are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R_z and R_y are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (Z), wherein (Z) is as defined above,

15 N(R_z)R_y, wherein R_z and R_y are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R_z and R_y are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (Z), wherein (Z) is as defined above,

N(R_z)-C(O)-R_y, wherein R_z and R_y are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,

20 N(H)-C(O)-N(R_z)R_y, wherein R_z and R_y are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R_z and R_y are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (Z), wherein (Z) is as defined above,

N(H)-C(O)-OR_z, wherein R_z is independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,

N(H)-S(O)₂(C₁-C₁₂ alkyl),

25 O-C(O)-N(R_z)R_y, wherein R_z and R_y are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R_z and R_y are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (Z), wherein (Z) is as defined above,

NO₂,

N₃,

30 N(H)-C(NR_x)-N(R_z)R_y, wherein R_z and R_y are independently hydrogen, C₁-C₄ alkyl, phenyl, or benzyl, or R_z and R_y are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (Z), wherein (Z) is as defined above, and R_x is hydrogen, hydroxy, methoxy, or CN,

CN,

halo,

35 S(O)-(C₁-C₁₂ alkyl),

S(O)₂(C₁-C₁₂ alkyl),

30 S(O)₂-N(R_z)-(R_y), wherein R_z and R_y are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R_z and R_y are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (Z), wherein (Z) is as defined above, and

40 S(O)₂CF₃.

[0136] Preferred substituents for substituted phenyl, substituted benzyl, substituted naphthyl (i.e., substituted 1-naphthyl or substituted 2-naphthyl), and preferred substituents at carbon atoms for substituted 5-membered, monocyclic heteroaryl, substituted 6-membered, monocyclic heteroaryl, and substituted 9- or 10-membered, fused-bicyclic heteroaryl are C₁-C₄ alkyl, halo, OH, O-C₁-C₄ alkyl, 1,2-methylenedioxy, CN, NO₂, N₃, NH₂, N(H)CH₃, N(CH₃)₂, C(O)CH₃, OC(O)-C₁-C₄ alkyl, C(O)-H, CO₂H, CO₂-(C₁-C₄ alkyl), C(O)-N(H)OH, C(O)NH₂, C(O)NHMe, C(O)N(Me)₂, NHC(O)CH₃, N(H)C(O)NH₂, SH, S-C₁-C₄ alkyl, C=CH, C(=NOH)-H, C(=NOH)-CH₃, CH₂OH, CH₂NH₂, CH₂N(H)CH₃, CH₂N(CH₃)₂, C(H)F-OH, CF₂-OH, S(O)₂NH₂, S(O)₂N(H)CH₃, S(O)₂N(CH₃)₂, S(O)-CH₃, S(O)₂CH₃, S(O)₂CF₃, or NHS(O)₂CH₃.

[0137] Especially preferred substituents are 1,2-methylenedioxy, methoxy, ethoxy, -O-C(O)CH₃, carboxy, carbomethoxy, and carboethoxy.

[0138] Further as shown above, substituted 5-membered, monocyclic heteroaryl and substituted 9- or 10-membered, fused-bicyclic heteroaryl may optionally be substituted at a nitrogen atom, instead of a carbon atom, with 1 of certain substituents of said 1 or 2 substituents. Substitution at said nitrogen atom is possible when a ring -N(H)- group is present. The substituent replaces the hydrogen atom in the -N(H)- group and is selected from:

C₁-C₁₂ alkyl, which may be straight or branched,

5 C_2 - C_{12} alkenyl, which may be straight or branched,
 C_2 - C_{12} alkynyl, which may be straight or branched,
 C_3 - C_{12} cycloalkyl,
 phenyl,
 10 substituted phenyl, wherein substituted phenyl is as defined above,
 benzyl,
 substituted benzyl, wherein substituted benzyl is as defined above,
 $C(O)-R_2$, wherein R_2 is as defined above,
 CN, and
 15 $S(O)_2R_2$, wherein R_2 is as defined above.

[0139] Illustrative examples of substituted 5-membered, monocyclic heteroaryl groups that are substituted at nitrogen include 1-methylimidazol-5-yl, 1-benzylpyrrol-2-yl, 1-acetyl-pyrazol-4-yl, 1-(4-fluorophenyl)-1,2,4-triazol-3-yl, and 2-decyl-tetrazol-5-yl.

15 [0140] Illustrative examples of substituted 9- or 10-membered, fused-bicyclic heteroaryl that may be substituted at nitrogen include 1-methylbenzimidazol-6-yl, 1-acetylbenztriazol-7-yl, 1-methanesulfonyl-indol-3-yl, 1-cyano-6-aza-indol-5-yl, and 1-(2,6-dichlorophenylmethyl)-benzpyrazol-3-yl.

[0141] Illustrative examples of:

20 (i) substituted phenyl include 4-methoxyphenyl, 2,6-difluorophenyl, 3-hydroxy-4-methylphenyl, 2-hydroxymethyl-3,4-dichloro-phenyl, 1,3-benzoxazol-5-yl, and 2-methoxy-4-nitrophenyl;
 (ii) substituted 1-naphthyl include 5-trifluoromethanesulfonylaminonaphth-1-yl and 2-(N-hydroxy-carboxamido)-naphth-1-yl; and
 25 (iii) substituted 2-naphthyl includes 5-trifluoromethanesulfonylaminonaphth-2-yl and 1-(N-hydroxy-carboxamido)-naphth-2-yl.

[0142] Illustrative examples of:

30 (i) substituted 5-membered, monocyclic heteroaryl include 3-chloro-thiophen-2-yl, 5-hexyl-furan-2-yl, 1-methyl-pyrrol-3-yl, 2-carboxy-pyrrol-1-yl, 1,2-dimethyl-imidazol-4-yl, 5-(4-carboethoxy-7-fluoro-heptyl)-isoxazol-3-yl, 4-trifluoromethyl-oxazol-2-yl, 2-hydroxy-thiazol-4-yl, 5-acetylaminotetrazol-1-yl, 5-(*tert*-butyl)-1,2,4-oxadiazol-3-yl, 3-cyano-1,2,4-triazol-1-yl, and 5-acetyl-pyrazol-3-yl;
 (ii) substituted 6-membered, monocyclic heteroaryl include 4,6-difluoropyridin-2-yl, 2-methyl-pyridin-4-yl, 4-azido-pyrimidin-2-yl, 6-ureidopyridazin-4-yl, and 5-methylthio-pyrazin-2-yl; and
 35 (iii) 9- or 10-membered, bicyclic heteroaryl include 6,7-dimethoxy-indol-2-yl, 1-propyl-indol-6-yl, 7-nitro-isoindol-2-yl, 1-benzyl-benzimidazol-2-yl, 4-chloro-benzimidazol-1-yl, 7-(2-propyl)-benztriazol-1-yl, 1-(2-hydroxyethyl)-benztriazol-5-yl, 4-iodo-quinolin-2-yl, 1-nitroisoquinolin-7-yl, 4-cyano-benzopyrimidin-2-yl, 4,5,6-trifluoro-benzoxazol-2-yl, 2-carboxy-benzothiophen-5-yl, and 4-methylsulfinyl-benzofuran-3-yl.

40 [0143] The term "1,2-methylenedioxy" means the diradical group $-O-CH_2-O-$, wherein the substituent 1,2-methylenedioxy is bonded to adjacent carbon atoms of the group which is substituted to form a 5-membered ring. Illustrative examples of groups substituted by 1,2-methylenedioxy include 1,3-benzodioxol-5-yl of formula B



50 which is a phenyl group substituted by 1,2-methylenedioxy.
 [0144] A fused-bicyclic group is a group wherein two ring systems share two, and only two, atoms.
 [0145] It should be appreciated that the groups heteroaryl or heterocyclene may not contain two adjacent ring atoms which are oxygen and/or sulfur atoms.
 55 [0146] The term "oxo" means $=O$. Oxo is attached at a carbon atom unless otherwise noted. Oxo, together with the carbon atom to which it is attached forms a carbonyl group (i.e., $C=O$).
 [0147] The term "heteroatom" means N, O, or S.
 [0148] The term "halo" means fluoro, chloro, bromo, or iodo.

[0149] The term "amino" means NH_2 .

[0150] The phrase "tertiary organic amine" means a trisubstituted nitrogen group wherein the 3 substituents are independently selected from $\text{C}_1\text{-C}_{12}$ alkyl, $\text{C}_3\text{-C}_{12}$ cycloalkyl, benzyl, or wherein two of the substituents are taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered, monocyclic heterocycle containing one nitrogen atom and carbon atoms, and the third substituent is selected from $\text{C}_1\text{-C}_{12}$ alkyl and benzyl, or wherein the three substituents are taken together with the nitrogen atom to which they are attached to form a 7- to 12-membered bicyclic heterocycle containing 1 or 2 nitrogen atoms and carbon atoms, and optionally a $\text{C}=\text{N}$ double bond when 2 nitrogen atoms are present. Illustrative examples of tertiary organic amine include triethylamine, diisopropylethylamine, benzyl diethylamino, dicyclohexylmethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (TED), and 1,5-diazabicyclo[4.3.0]non-5-ene.

[0151] The term "comprising," which is synonymous with the terms "including," "containing," or "characterized by," is inclusive or open-ended, and does not exclude additional, unrecited elements or method steps from the scope of the invention that is described following the term.

[0152] The phrase "consisting of" is closed-ended, and excludes any element, step, or ingredient not specified in the description of the invention that follows the phrase.

[0153] The phrase "consisting essentially of" limits the scope of the invention that follows to the specified elements, steps, or ingredients, and those further elements, steps, or ingredients that do not materially affect the basic and novel characteristics of the invention.

[0154] The phrase "pharmaceutical composition" means a composition suitable for administration in medical or veterinary use.

[0155] The phrase "in admixture" means in a state of being in a homogeneous or heterogeneous mixture. Preferred is a homogeneous mixture.

[0156] The term "patient" means a mammal. Preferred patients are humans, cats, dogs, cows, horses, pigs, and sheep.

[0157] The term " IC_{50} " means the concentration of test compound required to inhibit activity of a biological target, such as a receptor or enzyme, by 50%.

[0158] The phrase "autoimmune disease" means the diseases classified as "Highly probable" or "Probable" in Table 20-3. PUTATIVE AUTOIMMUNE DISORDERS of The Merck Manual of Diagnosis and Therapy, 16th edition, Robert Berkow ed., Merck Research Laboratories, Rahway, New Jersey, 1992:340, which is hereby incorporated herein by reference. Diseases classified as highly probable include, to name a few, systemic lupus erythematosus, Grave's disease, myasthenia gravis, insulin resistance, and autoimmune hemolytic anemia. Diseases classified as probable include, to name a few, rheumatoid arthritis, scleroderma with anti-collagen antibodies (Abs), pernicious anemia, and some cases of diabetes mellitus.

[0159] The phrase "hyper-immune disease" means diseases which involve an inappropriate, especially excessive, immune response. These diseases include asthma.

[0160] The phrases "connective tissue degradation" and "connective tissue breakdown" are synonymous and mean the cleavage of the macromolecular components of connective tissue such as, for example, collagens or proteoglycans.

[0161] The phrase "connective tissue" means a tissue of mesodermal origin rich in intercellular substance or interlacing processes with little tendency for the cells to come together in sheets or masses, especially connective tissue of stellate or spindle-shaped cells with interlacing processes that pervades, supports, and binds together other tissues and forms ligaments, tendons, or aponeuroses.

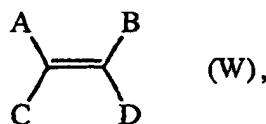
[0162] The phrases "extracellular matrix degradation" and "extracellular matrix breakdown" are synonymous and may be used interchangeably with the phrases "connective tissue degradation" and "connective tissue breakdown."

[0163] An example of connective tissue or extracellular matrix is cartilage, which lines the surface of bone in joints. Other connective tissue or extracellular matrix tissue includes the tissue that binds the cells of the skin, cell lining blood vessels, and multi-cellular structures of the heart, kidney, lung, and other organs.

[0164] The phrases "effective amount" and "therapeutically effective amount" are synonymous and mean an amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof, or a solvate thereof, sufficient to effect an improvement of the condition being treated when administered to a patient suffering from a disease that is mediated by MMP-13 and optionally from 0 to 12 additional MMP enzymes.

[0165] The term "(E)" means entgegen, and designates that the conformation about the double bond to which the term refers is the conformation having the two higher ranking substituent groups, as determined according to the Cahn-Ingold-Prelog ranking system, on opposite sides of the double bond. An (E) double bond is illustrated below by the compound of Formula (W)

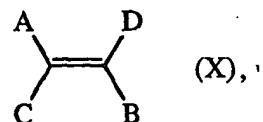
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wherein the two higher-ranking substituents are groups A and D.

10 [0166] The term "(Z)" means zusammen, and designates that the conformation about the double bond to which the term refers is the conformation having the two higher ranking substituent groups, as determined according to the Cahn-Ingold-Prelog ranking system, on the same side of the double bond. A (Z) double bond is illustrated below by the compound of Formula (X)

15



20 wherein the two higher-ranking substituents are groups A and D.

[0167] The phrase "pseudo aromatic" means similar to or derivable from an aromatic parent substance or tautomeric form thereof.

[0168] The phrase "inert atmosphere" means an atmosphere which consists essentially of nitrogen gas or argon gas, or mixtures thereof.

25 [0169] It should be appreciated that the matrix metalloproteinases include the following enzymes:

MMP-1, also known as interstitial collagenase, collagenase-1, or fibroblast-type collagenase;

MMP-2, also known as gelatinase A or 72 kDa Type IV collagenase;

MMP-3, also known as stromelysin or stromelysin-1;

30 MMP-7, also known as matrilysin or PUMP-1;

MMP-8, also known as neutrophil collagenase or polymorphonuclear-type ("PMN-type") collagenase;

MMP-9, also known as gelatinase B or 92 kDa Type IV collagenase;

MMP-10, also known as stromelysin-2;

MMP-11, also known as stromelysin-3;

35 MMP-12, also known as metalloelastase;

MMP-13, also known as collagenase-3;

MMP-14, also known as membrane-type ("MT") MMP-1 or MT-MMP-1;

MMP-15, also known as MT-MMP-2;

MMP-16, also known as MT-MMP-3;

40 MMP-17, also known as MT-MMP-4;

MMP-18; and

MMP-19.

45 [0170] As discussed above, one aspect of the present invention is novel compounds which are selective inhibitors of the enzyme MMP-13. A selective inhibitor of MMP-13, as used in the present invention, is a compound that is $\geq 10X$ more potent *in vitro* versus MMP-13 than versus at least one other matrix metalloproteinase enzyme such as, for example, MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, or MMP-14, or versus TACE. A preferred aspect of the present invention is novel compounds which are selective inhibitors of MMP-13 versus TACE and/or MMP-1.

50 [0171] Some of the compounds of the present invention may exist as tautomeric forms, which interchange via, for example, enolization and the like. All tautomeric forms are within the scope of the present invention.

[0172] Some compounds of the present invention have chiral centers, in which case all stereoisomers thereof, both enantiomers, diastereomers, and mixtures thereof, are within the scope of the present invention.

55 [0173] Some compounds of the present invention have alkenyl groups, which may exist as entgegen or zusammen conformations, in which case all geometric forms thereof, both entgegen and zusammen, *cis* and *trans*, and mixtures thereof, are within the scope of the present invention.

[0174] Some compounds of the present invention have cycloalkyl groups, which may be substituted at more than one carbon atom, in which case all geometric forms thereof, both *cis* and *trans*, and mixtures thereof, are within the scope of the present invention.

[0175] The compounds to be used in the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

[0176] The compounds of Formula I are capable of further forming pharmaceutically acceptable salts, including but not limited to acid addition and/or base salts.

[0177] Pharmaceutically acceptable acid addition salts of the compounds of Formula I include nontoxic salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, phosphorus, and the like, as well as the nontoxic salts derived from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, malate, tartrate, methanesulfonate, and the like. Also contemplated are the salts of amino acids such as arginate, gluconate, galacturonate, and the like; see, for example, Berge et al., "Pharmaceutical Salts," *J. of Pharmaceutical Science*, 1977;66:1-19.

[0178] The acid addition salts of the basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

[0179] Pharmaceutically acceptable base addition salts include nontoxic salts formed with metal cations, such as alkali and alkaline earth metal cations, or with organic (i.e., substituted) ammonium cations. Examples of suitable metal cations include sodium (Na^+) cation, potassium (K^+) cation, magnesium (Mg^{+2}) cation, calcium (Ca^{+2}) cation, and the like. Examples of suitable organic amines are *N,N*-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, *N*-methylglucamine, and procaine; see, for example, Berge et al., *Supra.*, 1977.

[0180] The base addition salts of acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base such as an alkali or alkaline earth metal hydroxide or an organic amine to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in a conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

[0181] All of these forms, including the free acids, or free bases, pharmaceutically acceptable salts, solvates, enantiomers, diastereomers, geometric isomers, and tautomers can be used in the compositions and methods of the present invention.

[0182] It should be appreciated that the above-described embodiments of the invention are not the only embodiments of the invention. All compounds described by the genus of compounds of Formula I are expected to be inhibitors of MMP-13 and useful for the invention methods and compositions. The embodiments of the invention include all possible compounds of Formula I and subsets of the genus of compounds of Formula I, which are permutations of combinations of the species of compounds described by Formula I, and their pharmaceutically acceptable salts thereof. All possible subsets of compounds of Formula I, and pharmaceutically acceptable salts thereof, are incorporated herein, and all pharmaceutical compositions comprising said permutations, and methods of using said permutations, are also incorporated herein. The instant invention should not be limited to the above particularly described embodiments because these subsets of compounds of Formula I are too numerous to practically describe herein.

[0183] The compounds of the present invention can be formulated and administered in a wide variety of oral and parenteral dosage forms, including transdermal and rectal administration. All that is required is that an MMP inhibitor be administered to a mammal suffering from a disease in an effective amount, which is that amount required to cause an improvement in the disease and/or the symptoms associated with such disease. It will be recognized to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt or solvate of a compound of Formula I. Formulation of the compounds of the present invention is fully described below.

[0184] Further, syntheses of the compounds of the present invention may utilize starting materials, intermediates, or reaction products that contain a reactive functional group. A reactive functional group may be protected during chemical reactions using protecting groups which render the reactive groups substantially inert to the reaction conditions. At a step in a synthesis of a compound of the present invention subsequent to the chemical reaction requiring a protecting group, and appropriate to the synthetic strategy employed, the protecting group may be removed. See, for example, *Protective Groups in Organic Synthesis*, 2nd ed., Greene T.W. and Wuts P.G., John Wiley & Sons, New York, NY, 1991, which is hereby incorporated by reference. Thus, for example, protecting groups such as the following

may be utilized to protect suitable amino, hydroxyl, and other groups of related reactivity: carboxylic acyl groups, such as formyl, acetyl, trifluoroacetyl; alkoxy carbonyl groups, such as ethoxycarbonyl, t-butoxycarbonyl (BOC), β,β,β -trichloroethoxycarbonyl (TCEC), β -idoethoxycarbonyl; aryloxycarbonyl groups, such as benzyloxycarbonyl (CBZ), p -methoxybenzyloxycarbonyl, phenoxy carbonyl; trialkyl silyl groups, such as trimethylsilyl and *t*-butyldimethylsilyl (TBDMS); and groups such as trityl, tetrahydropyranyl, vinyloxycarbonyl, σ -nitrophenylsulfonyl, diphenylphosphinyl, p -toluenesulfonyl, and benzyl may all be utilized. The protecting group may be removed, after completion of the synthetic reaction of interest, by procedures known to those skilled in the art. For example, a BOC group may be removed by acidolysis, a trityl group by hydrogenolysis, TBDMS by treatment with fluoride ions, and TCEC by treatment with zinc. Use of protecting groups in organic synthesis is well within the skill of the average artisan.

[0185] The compounds of the present invention can be prepared according to the various synthetic schemes that follow. Protecting groups may be used when appropriate throughout many of the schemes. Although specifically noted in certain schemes, the appropriate use and choice of protecting groups is well known by one skilled in the art, and is not limited to the specific examples below. It is also understood that such groups not only serve to protect chemically reactive sites, but also to enhance solubility or otherwise change physical properties. A good general reference for protecting group preparation and deprotection is "Protective Groups in Organic Synthesis" by Theodora Green, *supra*. A number of general reactions such as oxidations and reductions are not shown in detail but can be done by methods understood by one skilled in the art. General transformations are well reviewed in "Comprehensive Organic Transformation" by Richard Larock, and the series "Compendium of Organic Synthetic Methods" (1989) published by Wiley-Interscience.

[0186] It should be appreciated that reagents, solvents, and starting materials necessary for the preparation of the compounds of the invention may be purchased from a number of commercial sources or may be readily prepared by a number of methods well known to one of average skill in the art of organic chemistry. Further, reactions used to prepare the invention compounds can be carried out under a wide variety of conditions comprising solvents, reagents, catalysts, temperatures, time, atmosphere, and pressure.

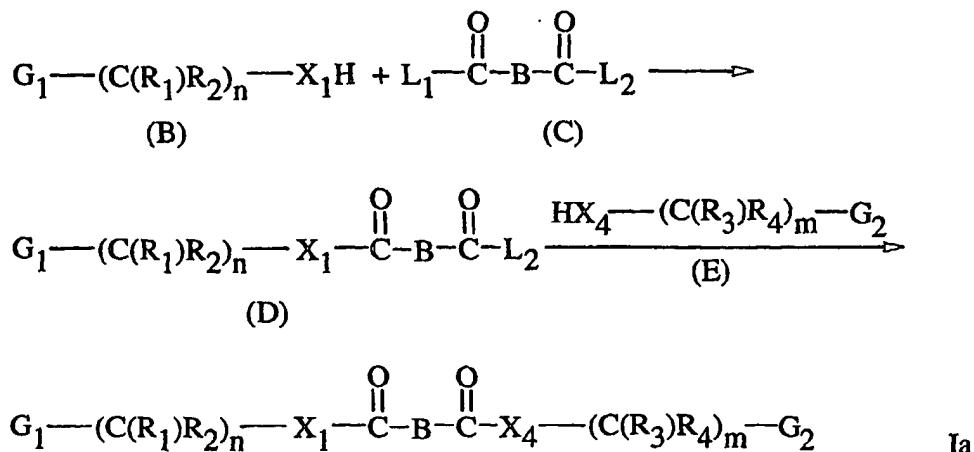
[0187] Many different methods may be used to prepare the invention compounds. However for purposes of practicing the invention, which comprises compounds, pharmaceutical compositions, and methods of preventing or treating patients with the disorders or diseases recited above, it does not matter how the compounds are made.

[0188] A compound of Formula I, or a pharmaceutically acceptable salt thereof, may be prepared by one of ordinary skill in the art of organic chemistry by adapting various synthetic procedures which are well-known in the art of organic chemistry. These synthetic procedures may be found in the literature in, for example, *Reagents for Organic Synthesis*, by Fieser and Fieser, John Wiley & Sons, Inc., New York, 2000; *Comprehensive Organic Transformations*, by Richard C. Larock, VCH Publishers, Inc., New York, 1989; the series *Compendium of Organic Synthetic Methods* (1989) by Wiley-Interscience; the text *Advanced Organic Chemistry*, 5th edition, by Jerry March, Wiley-Interscience, New York (2001); or the *Handbook of Heterocyclic Chemistry*, by Alan R. Katritzky, Pergamon Press Ltd., London, (1985), to name a few. Alternatively, a skilled artisan may find methods useful for preparing the invention compounds in the chemical literature by searching widely available databases such as, for example, those available from the *Chemical Abstracts Service*, Columbus, Ohio, or *MDL Information Systems GmbH* (formerly *Beilstein Information Systems GmbH*), Frankfurt, Germany.

[0189] Preparations of the compounds of the present invention may use starting materials, reagents, solvents, and catalysts that may be purchased from commercial sources or they may be readily prepared by adapting procedures in the references or resources cited above. Commercial sources of starting materials, reagents, solvents, and catalysts useful in preparing invention compounds include, for example, *The Aldrich Chemical Company*, and other subsidiaries of Sigma-Aldrich Corporation, St. Louis, Missouri, *BACHEM*, BACHEM A.G., Switzerland, or *Lancaster Synthesis Ltd.*, United Kingdom.

[0190] Typical syntheses of the invention compounds are illustrated in the schemes below.

Scheme 1



20 [0191] Scheme 1 outlines a preparation of a compound of Formula Ia, which is a compound of Formula I wherein Q₁ is X₁-C(O), Q₂ is C(O)-X₄, and G₁, G₂, R₁, R₂, R₃, R₄, n, m, and B are as defined above for Formula I. In Scheme 1, a compound of formula (B), wherein G₁, R₁, R₂, n, and X₁ are as defined above for Formula I, is allowed to react with a compound of formula (C), wherein L₁ is a leaving group useful in coupling reactions of carboxylic acids such as, for example OH, Cl, F, O-C(O)C(CH₃)₃, O-(pentafluorophenyl), imidazol-1-yl, benzotriazol-1-yl, and the like and L₂ is as defined for L₁ or L₂ is O-R_L, wherein R_L is methyl, ethyl, *tert*-butyl, benzyl, and the like, to give a compound of formula (D), which is a carboxylic ester (when X₁ is O) or an amide (when X₁ is NH). The reaction is a coupling reaction between an alcohol (X₁ is O) or an amine (X₁ is NH) of formula (B) with a carboxylic acid, or an activated derivative thereof, of formula (C), which is a reaction with many variations that are well known in the art of organic chemistry. For example, carboxylic esters and amides may be formed by coupling an alcohol or amine, respectively, with a carboxylic acid using a coupling reagent or reagent mixture such as, for example, N,N'-carbonyldiimidazole (CDI), N, N'-dicyclohexylcarbodiimide (DCC), P(Ph)₃ and diethylazodicarboxylate, bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), POCl₃, Ti(Cl)₄, and many more, in an aprotic solvent such as, for example, dichloromethane, tetrahydrofuran (THF), dimethylformamide (DMF), dioxane, ethyl acetate, ethyl ether, acetonitrile, and the like. The compound of formula (D) wherein L₂ is O-R_L, may be deprotected to give a compound of formula (D) wherein L₂ is as defined above for L₁, using well-known conditions for converting a carboxylic ester to a carboxylic acid such as, for example, saponification with an alkali or alkaline metal hydroxide such as, for example NaOH, KOH, or Mg(OH)₂, hydrolysis with an aqueous acid such as, for example, trifluoroacetic acid (TFA), aqueous sulfuric acid, aqueous amberlyst-15 resin, aqueous hydrochloric acid, and the like, or cleavage with a non-aqueous acid or reagent when L₂ is O-(*tert*-butyl) or O-benzyl such as, for example, hydrogen chloride or TFA in dichloromethane, hydrogen bromide in acetic acid, trimethylsilyliodide in dichloromethane, and the like. Alternatively when L₂ is O-benzyl, deprotection may be carried out using hydrogenation conditions such as, for example, hydrogen gas at 50 psi in the presence of a hydrogenation catalyst such as, for example, about 5% palladium on carbon or about 10% palladium on barium sulfate. In any event, in a manner similar to that described above for the coupling of a compound of formula (B) with a compound of formula (C), a compound of formula (D) is coupled with a compound of formula (E), wherein G₂, R₃, R₄, m, and X₄ are as defined above for Formula I, to give a compound of the present invention of Formula Ia. An alternative preparation of a compound of the present invention of Formula Ia is outlined below in Scheme 8. Compounds of the present invention of Formulas II and III may be prepared by the method outlined in Scheme 1.

25 [0192] Further, a preparation of a compound of Formula Ib, which is a compound of the present invention of Formula I wherein Q₁ is C(O)-X₂, Q₂ is C(O)-X₄, and G₁, G₂, R₁, R₂, R₃, R₄, n, m, and B are as defined above for Formula I, is outlined below in Scheme 2.

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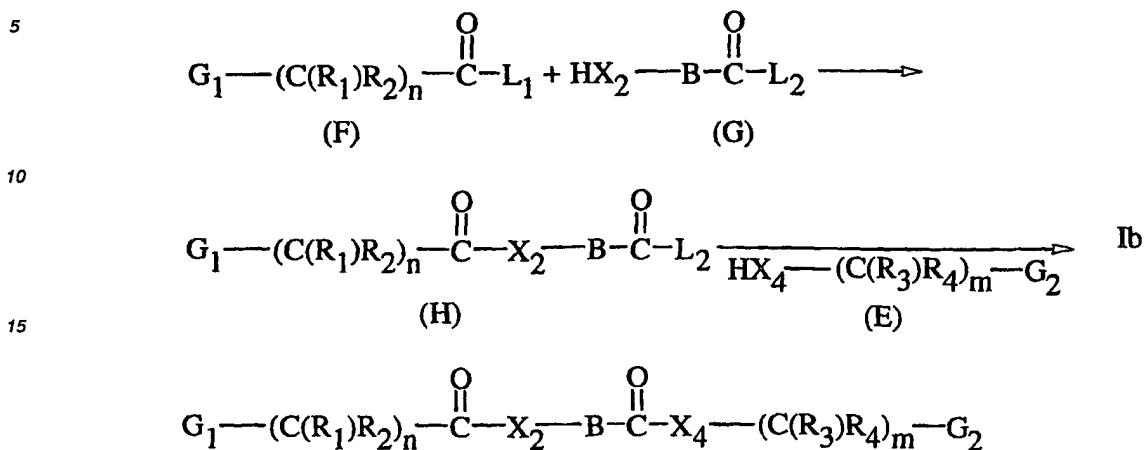
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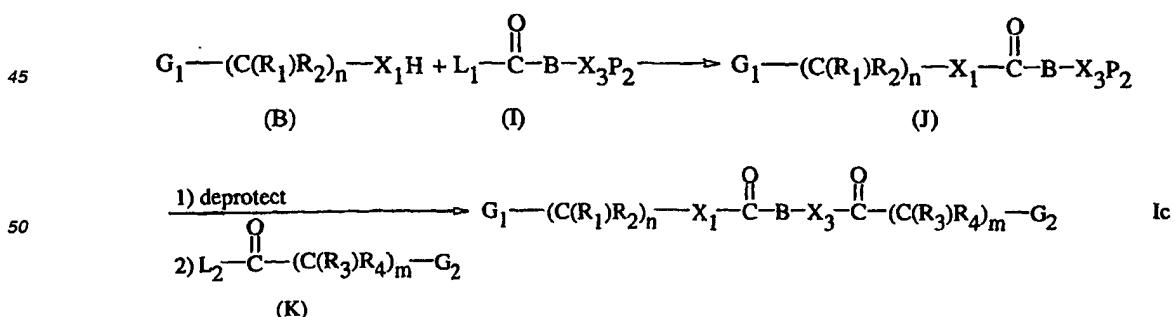
Scheme 2



[0193] In Scheme 2, a compound of formula (F), wherein L_1 is a leaving group as defined above for Scheme 1 and G_1 , R_1 , R_2 , and n are as defined above for Formula I, is allowed to react with a compound of formula (G), wherein L_2 is as defined above for Scheme 1 and X_2 and B are as defined above for Formula I, to give a compound of formula (H). The reaction is a coupling reaction between an alcohol (X_2 is O) or an amine (X_2 is NH) of formula (G) with a carboxylic acid, or an activated derivative thereof, of formula (F), which may be accomplished using the conditions described above for Scheme 1 for the coupling of a compound of formula (B) with a compound of formula (C). The compound of formula (H) wherein L_2 is $O-R_L$, may be deprotected to give a compound of formula (D) wherein L_2 is as defined above for L_1 , using the well-known conditions for converting a carboxylic ester to a carboxylic acid described above in Scheme 1. In any event, in a manner similar to that described above for the coupling of a compound of formula (B) with a compound of formula (C) in Scheme 1, a compound of formula (H) is coupled with a compound of formula (E), wherein G_2 , R_3 , R_4 , m , and X_4 are as defined above for Formula I, to give a compound of the present invention of Formula Ib. Compounds of the present invention of Formula IV may be prepared according to the method outlined in Scheme 2.

[0194] Further, a preparation of a compound of Formula Ic, which is a compound of the present invention of Formula I wherein Q_1 is $X_1-C(O)$, Q_2 is $X_3-C(O)$, and G_1 , G_2 , R_1 , R_2 , R_3 , R_4 , n , m , and B are as defined above for Formula I, is outlined below in Scheme 3.

Scheme 3



[0195] In Scheme 3, a compound of formula (B), which is as described above for Scheme 1, is allowed to react with a compound of formula (I), wherein L_1 is a leaving group as defined above for Scheme 1, X_3 , and B are as defined above for Formula I, and P_2 is an alcohol (X_2 is O) or amine (X_2 is NH) protecting group such as, for example, $C(O)C_6H_5$.

CH₃, benzyl, trimethylsilyl, tetrahydropyran-2-yl, and the like when X₃ is O, or *tert*-butoxycarbonyl (BOC), benzyloxycarbonyl (CBZ), benzyl, 9-fluorenylmethyloxycarbonyl (FMOC), and the like when X₃ is NH, to give a compound of formula (J). The reaction is a coupling reaction between an alcohol (X₃ is O) or an amine (X₃ is NH) of formula (B) with a carboxylic acid, or an activated derivative thereof, of formula (I), which may be accomplished using the conditions

5 described above for Scheme 1 for the coupling of a compound of formula (B) with a compound of formula (C). A compound of formula (J) is then deprotected using conditions well known in the art of organic chemistry for the deprotection of alcohols or amines. Methods for deprotection may be found above and in, for example, Greene and Wuts P. G., *Supra*, 1991. Once a compound of formula (J) is deprotected, it is allowed to react with a compound of formula (K), wherein L₂ is a protecting group as described above for Scheme 1, and R₃, R₄, m, and G₂ are as defined above for

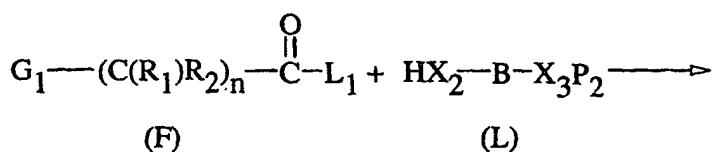
10 Formula I, in a manner similar to that described above in Scheme 1 for the coupling of a compound of formula (B) with a compound of formula (C), to give a compound of the present invention of Formula Ic.

[0196] Further, a preparation of a compound of Formula Id, which is a compound of the present invention of Formula I wherein Q₁ is C(O)-X₂, Q₂ is X₃-C(O), and G₁, G₂, R₁, R₂, R₃, R₄, n, m, and B are as defined above for Formula I, is outlined below in Scheme 4.

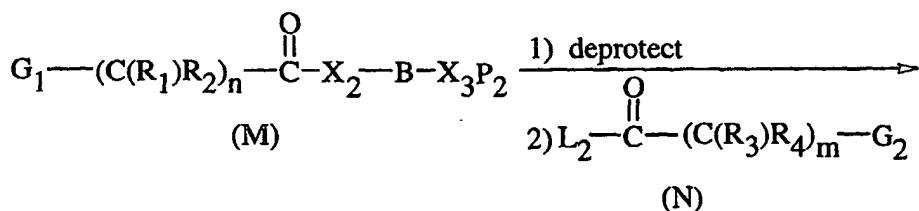
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Scheme 4

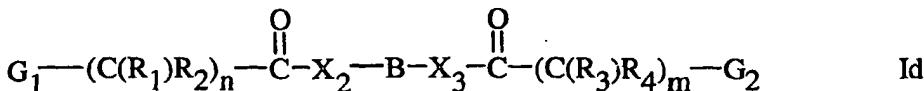
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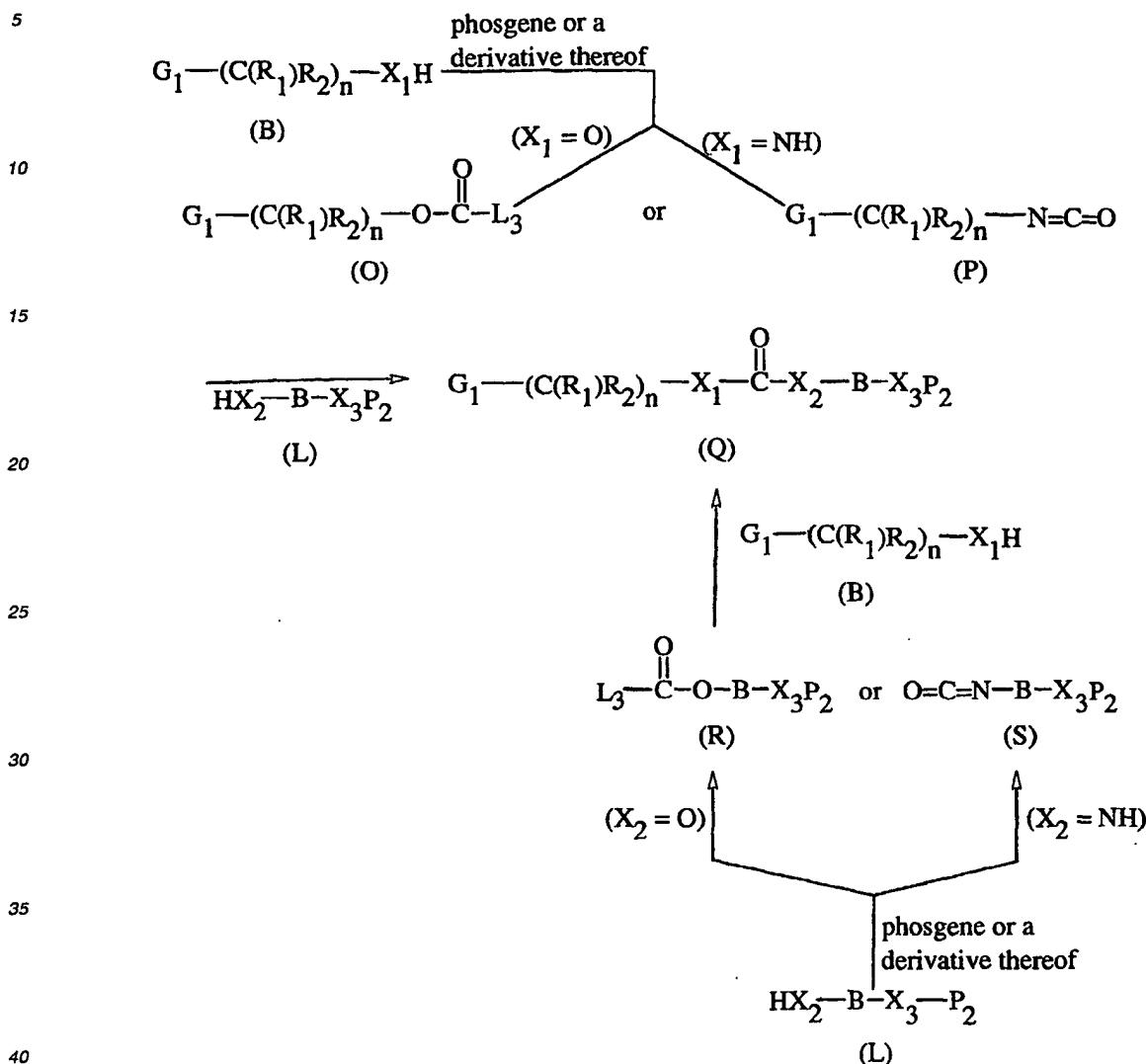


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[0197] In Scheme 4, a compound of formula (F), which is as described above for Scheme 2, is allowed to react with a compound of formula (L), wherein X₂, X₃, and B are as described above for Formula I and P₂ is as described above for Scheme 3, to give a compound of formula (M). The reaction is a coupling reaction between an alcohol (X₃ is O) or an amine (X₃ is NH) of formula (L) with a carboxylic acid, or an activated derivative thereof, of formula (F), which may be accomplished using the conditions described above for Scheme 1 for the coupling of a compound of formula (B) with a compound of formula (C). A compound of formula (M) is then deprotected using conditions well-known in the art of organic chemistry for the deprotection of alcohols or amines, as described above for the deprotection of a compound of Formula (J) in Scheme 3. Once a compound of formula (M) is deprotected, it is allowed to react with a compound of formula (N), wherein L₂ is a protecting group as described above for Scheme 1, and R₃, R₄, m, and G₂ are as defined above for Formula I, in a manner similar to that described above in Scheme 1 for the coupling of a compound of formula (B) with a compound of formula (C), to give a compound of the present invention of Formula Id.

[0198] Further, a preparation of a compound of Formula Id, which is a compound of the present invention of Formula I wherein Q₁ is X₁-C(P)-X₂, Q₂ is X₃-C(O)-X₄, and G₁, G₂, R₁, R₂, R₃, R₄, n, m, and B are as defined above for Formula I, is outlined below in Schemes 5 and 6. Scheme 5 outlines two preparations of an intermediate compound of formula (Q) and Scheme 6 outlines the conversion of a compound of Formula (Q) to a compound of the present invention of Formula Id.

Scheme 5

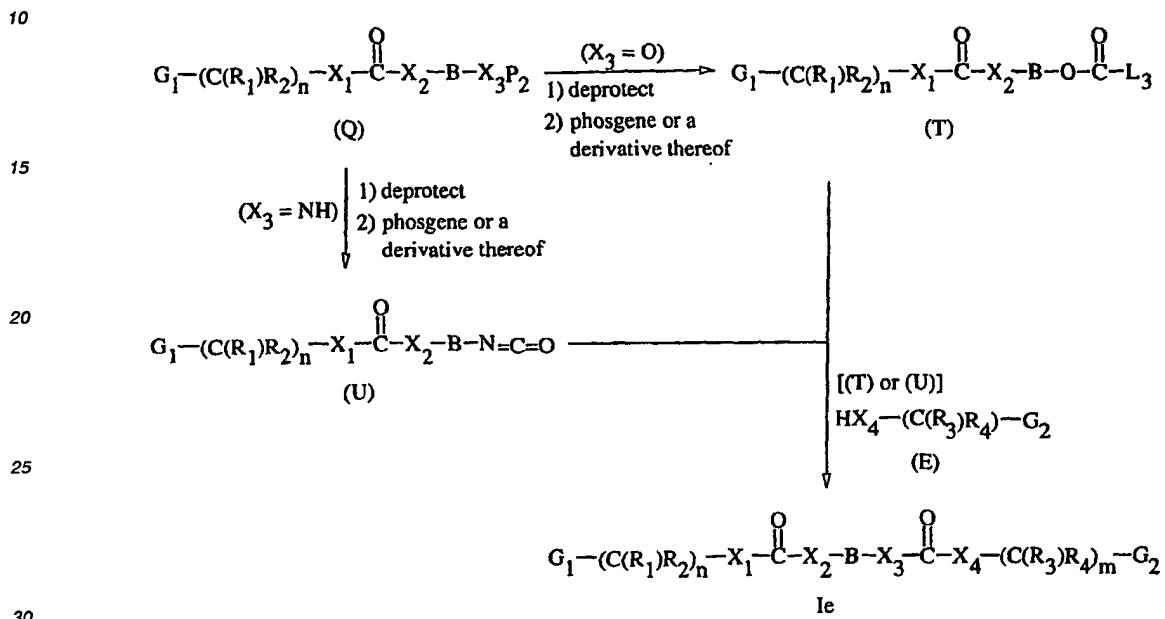


[0199] In Scheme 5, a compound of formula (B), which is as described above for Scheme 1, is allowed to react with phosgene, or a derivative thereof such as, for example, triphosgene or pentafluorophenyl chloroformate, in an aprotic solvent such as, for example, dichloromethane, THF, ethyl ether, acetonitrile, and the like, optionally in the presence of from 1 to 5 mole-equivalents of a suitable base such as pyridine or a tertiary organic amine, to give, when X_1 is O, a compound of formula (O), wherein L_3 is chloro, pentafluorophenoxy, and the like and G_1 , R_1 , R_2 , and n are as defined above for Formula I, or, when X_1 is NH, a compound of formula (P), wherein G_1 , R_1 , R_2 , and n are as defined above for Formula I. A compound of formula (O) or formula (P) is allowed to react with a compound of formula (L), which is as described above for Scheme 4, in an aprotic solvent such as, for example, dichloromethane, THF, ethyl ether, acetonitrile, and the like, optionally in the presence of from 1 to 5 mole-equivalents of a suitable base such as a anhydrous potassium carbonate, pyridine, or a tertiary organic amine, to give a compound of formula (Q), wherein P_2 is as defined above for Scheme 3 and G_1 , R_1 , R_2 , n , X_1 , X_2 , B , and X_3 are as defined above for Formula I, which compound of Formula (Q) is a carbonate when $X_1=X_2=O$, a carbamate when X_1 or X_2 is O and the other of X_1 and X_2 is NH, or a urea when $X_1=X_2=NH$. Alternatively, a compound of formula (Q) may be prepared by reaction of compound of formula (R), wherein L_3 and P_2 are as described above and B and X_3 are as defined above for Formula I, or a compound of formula (S), wherein P_2 is as defined above and B and X_3 are as defined above for Formula I, with a compound of Formula (B) in a manner similar to that described above for the reaction of a compound of formula (O) or (P), respectively.

with a compound of Formula (L). Compounds of formulas (R) or (S) may be prepared from a compound of formula (L) in a manner similar to that described above for the preparation of a compound of formulas (O) or (P), respectively, from a compound of formula (B).

5 [0200] As mentioned above, Scheme 6 outlines the conversion of a compound of formula (Q) to a compound of the present invention of Formula Ie.

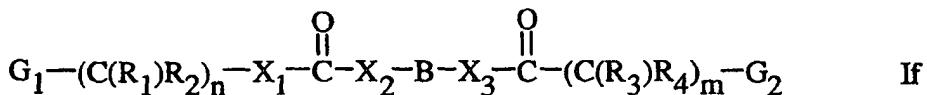
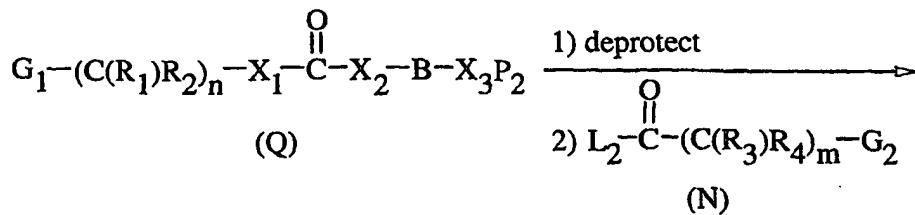
Scheme 6



[0201] In Scheme 6, a compound of formula (Q), prepared according to Scheme 5 above, is deprotected in a manner similar to that described above for the deprotection of a compound of formula (M) in Scheme 4. Once a compound of formula (Q) is deprotected, it is allowed to react with phosgene, or a derivative thereof, to give, when X_3 is O, a compound of formula (T), wherein L_3 is as described above for Scheme 5 and $\text{G}_1, \text{R}_1, \text{R}_2, n, \text{X}_1, \text{X}_2, \text{B}$ are as defined above for Formula I, or, when X_3 is NH, a compound of formula (U), wherein $\text{G}_1, \text{R}_1, \text{R}_2, n, \text{X}_1, \text{X}_2$, and B are as defined above for Formula I. The latter reaction is in a manner similar to that described above for Scheme 5 for the reaction of a compound of formula (B) with phosgene, or a derivative thereof, to give a compound of formula (O) or (P), respectively.

35 [0202] Further, a preparation of a compound of Formula Ie, which is a compound of the present invention of Formula I where Q_1 is $\text{X}_1-\text{C}(\text{O})-\text{X}_2$, Q_2 is $\text{X}_3-\text{C}(\text{O})$, and $\text{G}_1, \text{G}_2, \text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, n, m$, and B are as defined above for Formula I, is outlined below in Scheme 7.

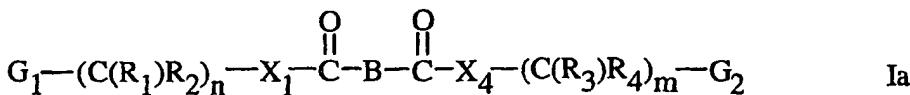
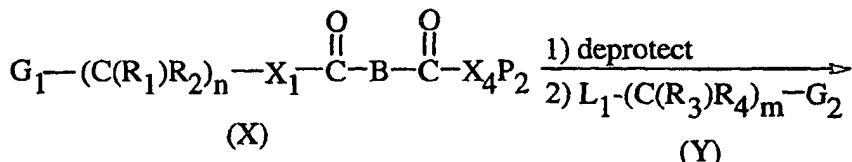
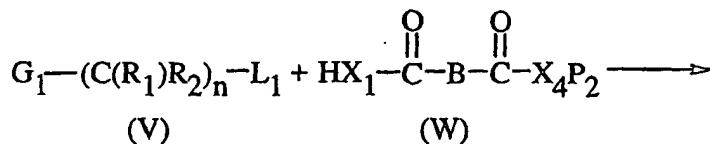
Scheme 7



[0203] In Scheme 7, a compound of formula (Q), prepared according to Scheme 5, is deprotected according to Scheme 6, and the deprotected compound is allowed to react via a coupling reaction with a compound of formula (N), prepared according to Scheme 4, to give a compound of Formula Ia. The deprotection/coupling reaction sequence is done in a manner similar to the deprotection/reaction of a compound of formula (M) with a compound of formula (N) as described for Scheme 4. Compounds of the present invention of Formula V may be prepared according to the method of Scheme 7.

[0204] Further, a preparation of a compound of Formula Ia, which is a compound of the present invention of Formula I wherein Q₁ is X₁-C(O), Q₂ is C(O)-X₃, and G₁, G₂, R₁, R₂, R₃, R₄, n, m, and B are as defined above for Formula I, is outlined below in Scheme 8.

Scheme 8



[0205] In Scheme 8, a compound of formula (V), wherein L_1 is as described above for Scheme 1 and G_1 , R_1 , R_2 , and n are as defined above for Formula I, is allowed to react with a compound of formula (W), wherein P_2 is as described above for Scheme 3 and X_1 , X_4 , and B are as defined above for Formula I, to give a compound of formula (X). The reaction is carried out in a solvent such as, for example, THF, isopropanol, ethyl ether, dichloromethane, DMF, dimethylsulfoxide (DMSO), acetonitrile, acetone, and the like, optionally in the presence of from 1 to 4 mole-equivalents of a suitable base, such as, for example, n-butyl lithium, a tertiary organic amine, pyridine, sodium carbonate, potassium *tert*-butoxide, sodium hydride, and the like. A compound of formula (X) is deprotected according to the procedure described above for Scheme 3 for the deprotection of a compound of formula (J), and the deprotected intermediate is allowed to react with a compound of formula (Y), wherein L_1 is as defined above for Scheme 1 and R_3 , R_4 , m , and G_2 .

are as defined above for Formula I, to give a compound of the present invention of Formula Ia. The deprotection/coupling reaction sequence is done in a manner similar to the deprotection/reaction of a compound of formula (M) with a compound of formula (N) as described for Scheme 4. The synthetic strategy employed in Scheme 8 may also be adapted for the preparation of compounds of the present invention of Formulas Ib and Ic. Compounds of the present invention of Formulas II and III may be prepared according to the method of Scheme 8.

[0206] The following detailed examples further illustrate the synthesis of typical invention compounds of Formula I. The examples are representative only, and are not to be construed as limiting the invention in any respect.

[0207] The following specific starting materials can be prepared using literature procedures, according to the following references.

[0208] For the preparation of 3-Methoxy-2,5-thiophenedicarboxylic acid (Examples 3 and 4), see *Chem. Ber.*, 1954; 87:841.

[0209] For the preparation of 2,4-Thiophenecarboxylic acid (Examples 5 and 6), see *Org. Prep. Proc. Int.*, 1971;3:295.

[0210] For the preparation of N-Methyl-2,4-pyrroledicarboxylic acid (Examples 7 and 8), see *Chem. Ber.*, 1970;103: 3196.

[0211] For the preparation of 1,3-Diisopropyl-2-benzylisourea (Example 9), see *Liebigs Ann. Chem.*, 1965;685:161.

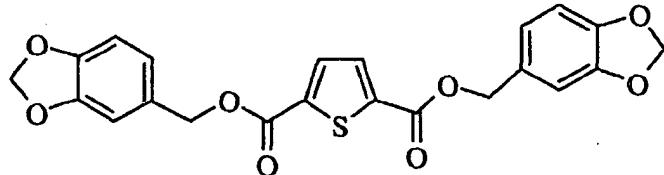
[0212] For the preparation of 5-Methyl-4-amino-thiophene-2-carboxylic acid (Examples 10 and 12), see *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984;33:2338.

[0213] For the preparation of 5-Methyl-4-nitro-thiophene-2-carboxylic acid methyl ester (Example 14), see *J. Am. Chem. Soc.*, 1951;73:3812.

[0214] For the preparation of 5-Methyl-4-nitro-thiophene-2-carboxylic acid (Examples 9, 15, and 16), see *J. Chem. Soc.*, 1980;Perk 2:1331.

EXAMPLE 1

[0215]

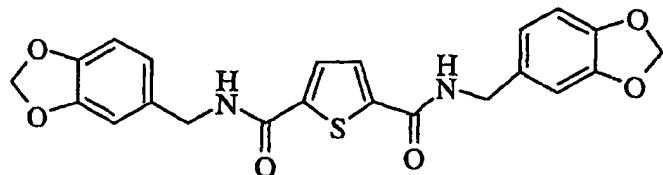


35 Thiophene-2,5-dicarboxylic acid di-1,3-benzodioxol-5-ylmethyl ester

[0216] Cesium carbonate (4.7 g, 14.4 mmol) was added to a stirred solution of 2,5-thiophenedicarboxylic acid in dimethylformamide (35 mL) under an inert atmosphere at room temperature. After 5 minutes, a solution of 3,4-methylenedioxybenzyl chloride in dichloromethane (3.7 mL, 14.3 mmol) was added. After 24 hours the mixture was stirred into water (150 mL) and acidified with dilute aqueous HCl. After several hours, the precipitate was filtered off, rinsed with water, and dried to afford 0.6 g of thiophene-2,5-dicarboxylic acid di-1,3-benzodioxol-5-ylmethyl ester. Recrystallization of a sample from ethanol gave product with a mp 141-148°C.

EXAMPLE 2

[0217]



55 Thiophene-2,5-dicarboxylic acid bis-[(1,3-benzodioxol-5-ylmethyl)-amide]

[0218] 1,1'-Carbonyldiimidazole (1.2 g, 7.4 mmol) was added to a stirred solution of 2,5-thiophene-dicarboxylic acid (0.5 g, 3.0 mmol) in dimethylformamide (25 mL) under an inert atmosphere, and the mixture was heated to 55°C to 60°C. After 30 minutes, the mixture was allowed to cool and piperonylamine (1.05 g, 6.7 mmol) was added. The mixture

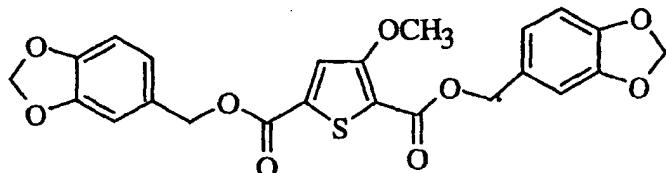
was reheated to 55°C to 60°C. After 3 hours, the mixture was allowed to cool, and was poured into water (250 mL), and the aqueous mixture was stirred. After several hours, the precipitate was filtered off, rinsed with water, and dried to afford 1.2 g of thiophene-2,5-dicarboxylic acid bis-[(1,3-benzodioxol-5-ylmethyl)-amide]. Recrystallization of a sample from ethanol gave product with a mp 207-209°C.

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EXAMPLE 3

[0219]

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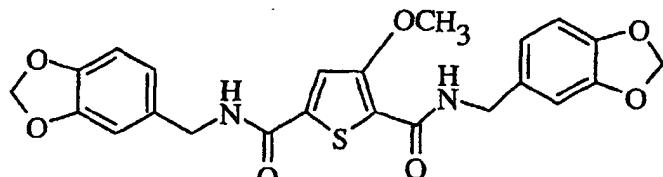
3-Methoxy-thiophene-2,5-dicarboxylic acid di-1,3-benzodioxol-5-ylmethyl ester

[0220] The title compound was prepared according to the procedure of Example 2 using carbonyldiimidazole (0.8 g, 4.8 mmol), 3-methoxy-2,5-thiophene-dicarboxylic acid (0.4 g, 2.0 mmol), and piperonyl alcohol (0.62 g, 4.0 mmol). Acidification of the aqueous workup mixture with dilute hydrochloric acid prior to filtration afforded 0.8 g of 3-methoxy-thiophene-2,5-dicarboxylic acid di-1,3-benzodioxol-5-ylmethyl ester. Recrystallization of a sample from acetonitrile gave product with a mp 153-155°C.

25 EXAMPLE 4

[0221]

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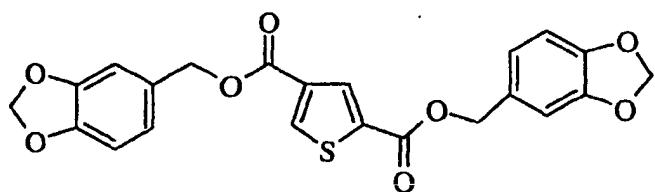
3-Methoxy-thiophene-2,5-dicarboxylic acid bis-[(1,3-benzodioxol-5-ylmethyl)-amide]

[0222] The title compound was prepared according to the procedure of Example 2 using carbonyldiimidazole (1.0 g, 6.2 mmol), 3-methoxy-2,5-thiophenedicarboxylic acid (0.5 g, 2.5 mmol), and piperonylamine (0.85 g, 5.6 mmol) to afford 1.05 g of 3-methoxy-thiophene-2,5-dicarboxylic acid bis-[(1,3-benzodioxol-5-ylmethyl)-amide]. Recrystallization of a sample from dimethylformamide gave product with a mp 191-195°C.

EXAMPLE 5

45 [0223]

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Thiophene-2,4-dicarboxylic acid di-1,3-benzodioxol-5-ylmethyl ester

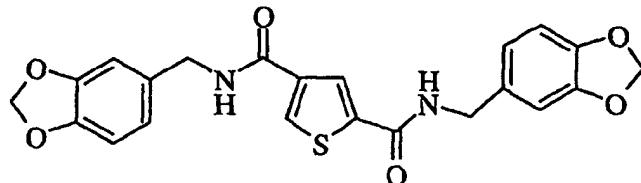
[0224] The title compound was prepared according to the procedure described for Example 2 using carbonyldiimidazole (1.1 g, 6.8 mmol), 2,4-thiophene-dicarboxylic acid (0.5 g, 2.9 mmol) and piperonyl alcohol (0.45 g, 2.9 mmol).

Acidification of the aqueous workup mixture with dilute hydrochloric acid prior to filtration afforded 0.71 g of thiophene-2,4-dicarboxylic acid bis-[(1,3-benzodioxol-5-ylmethyl)-ester]. Recrystallization of a sample from methanol followed by trituration in ethyl acetate then ether and drying gave product with a mp 164-165°C.

5 EXAMPLE 6

[0225]

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Thiophene-2,4-dicarboxylic acid bis-[(1,3-benzodioxol-5-ylmethyl)-amide]

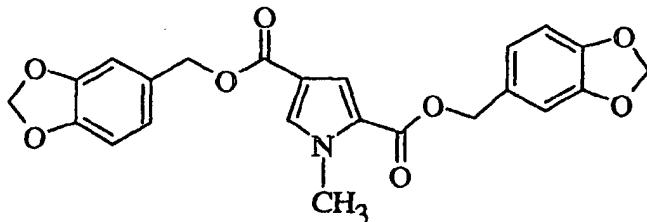
20 [0226] The title compound was prepared according to the procedure described for Example 2 using carbonyldiimidazole (1.2 g, 7.4 mmol), 2,4-thiophene-dicarboxylic acid (0.5 g, 3.0 mmol), and piperonylamine (1.05 g, 6.7 mmol) to afford 1.2 g of thiophene-2,4-dicarboxylic acid bis-[(1,3-benzodioxol-5-ylmethyl)-amide]. Recrystallization of a sample from ethanol gave product with a mp 174-175°C.

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EXAMPLE 7

[0227]

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1-Methyl-1H-pyrrole-2,4-dicarboxylic acid di-1,3-benzodioxol-5-ylmethyl ester

40 [0228] 1,1'-Carbonyldiimidazole (1.3 g, 8.0 mmol) was added to a stirred solution of N-methyl-2,4-pyrrole-dicarboxylic acid (0.6 g, 3.5 mmol) in dimethylformamide (6 mL) under an inert atmosphere and heated to 40°C. After 30 minutes the mixture was allowed to cool, and piperonyl alcohol (1.1 g, 7.1 mmol) was added. The mixture was heated to 60°C for 3 hours, then poured into water (100 mL), stirred, and acidified with 4N HCl. The resulting mixture was extracted twice with ethyl acetate (60 mL), and the combined extracts were washed successively with water, 0.5 M aqueous sodium bicarbonate, and saturated brine, then dried over MgSO₄. The solvent was removed under reduced pressure, and the residue was dissolved in a minimum of hot acetonitrile, cooled, and filtered. The filtrate was taken to dryness under reduced pressure, and the residual product (0.9 g) was chromatographed on a column of silica gel under nitrogen pressure, eluting with ethyl acetate/petroleum ether 2:3. Evaporation of the appropriate fractions and drying afforded 1-methyl-1H-pyrrole-2,4-dicarboxylic acid di-1,3-benzodioxol-5-ylmethyl ester; mp 103-110°C.

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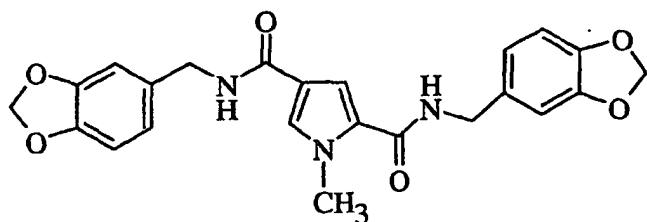
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EXAMPLE 8

[0229]

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15 1-Methyl-1H-pyrrole-2,4-dicarboxylic acid bis-[(1,3-benzodioxol-5-ylmethyl)-amide]

[0230] The title compound was prepared according to the procedure described for Example 2 using carbonyldiimidazole (1.2 g, 7.4 mmol), N-methyl-2,4-pyrroledicarboxylic acid (0.5 g, 3.0 mmol) and piperonylamine (1.1 g, 7.3 mmol) to afford 1.1 g of 1-methyl-1H-pyrrole-2,4-dicarboxylic acid bis-[(1,3-benzodioxol-5-ylmethyl)-amide]. Recrystallization of a sample from acetonitrile gave product with a mp 147-152°C.

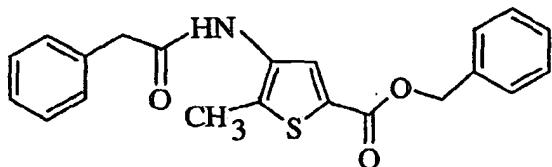
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EXAMPLE 9

[0231]

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5-Methyl-4-phenylacetylaminothiophene-2-carboxylic acid benzyl ester

35 Step 1: 5-Methyl-4-nitro-thiophene-2-carboxylic acid benzyl ester

[0232] A mixture of 5-methyl-4-nitro-thiophene-2-carboxylic acid (1.0 g, 5.3 mmol) and 1,3-diisopropyl-2-benzylisourea (1.54 g, 6.4 mmol) in acetonitrile (25 mL) was stirred under an inert atmosphere and heated to reflux. After 48 hours the mixture was cooled, the solvent was removed under reduced pressure, and the residue was triturated in diethyl ether and cooled. The precipitate was filtered off and rinsed with cold ether. The filtrate and washings were combined, and rotary evaporated under reduced pressure. The resulting residue was dissolved in a minimum of ethyl acetate, and the solution was filtered through a column of silica gel, eluting with more ethyl acetate. The filtrate was rotary evaporated to dryness under reduced pressure to afford 1.2 g of 5-methyl-4-nitro-thiophene-2-carboxylic acid benzyl ester. A sample was chromatographed on silica gel in ether/petroleum ether 1:1, then recrystallized from ethanol to give product with a mp 57-58°C.

45 Step 2: 5-Methyl-4-amino-thiophene-2-carboxylic acid benzyl ester

[0233] Sponge nickel (0.6 g water wet) was added to a solution of 5-methyl-4-nitro-thiophene-2-carboxylic acid benzyl ester (0.93 g, 3.4 mmol), prepared as described in Step 1 above, in tetrahydrofuran (50 mL), and the mixture was hydrogenated at room temperature under hydrogen atmosphere at a starting pressure of 50 psi. After a reaction time of 2.4 hours, the pressure was released and the mixture filtered. The slurry was rinsed with tetrahydrofuran, and the filtrate was stripped of solvent under reduced pressure, leaving 0.9 g of 5-methyl-4-amino-thiophene-2-carboxylic acid benzyl ester as an oil.

55

Step 3: 5-Methyl-4-phenylacetylaminothiophene-2-carboxylic acid benzyl ester

[0234] Phenylacetyl chloride (0.26 g, 1.7 mmol) was added to a stirred solution of 5-methyl-4-amino-thiophene-2-car-

boxylic acid benzyl ester (0.4 g, 1.6 mmol), prepared as described above in Step 2, and diisopropylethylamine (0.26 g, 2.0 mmol) in tetrahydrofuran (15 mL) under an inert atmosphere at room temperature. After 18 hours, the mixture was diluted with water (100 mL) and acidified with aqueous HCl. The precipitate was filtered off, rinsed with water, then ethanol, then ether, and dried to afford 0.3 g of 5-methyl-4-phenylacetyl amino-thiophene-2-carboxylic acid benzyl ester. Recrystallization of a sample from acetonitrile gave product with a mp 173-174°C.

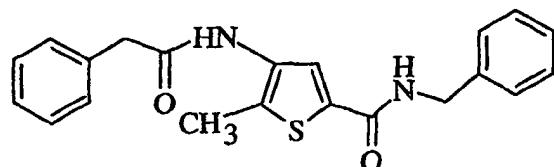
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EXAMPLE 10

[0235]

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5-Methyl-4-phenylacetyl amino-thiophene-2-carboxylic acid benzylamide

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Step 1: 5-Methyl-4-phenylacetyl amino-thiophene-2-carboxylic acid

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[0236] Diisopropylethylamine (3.33 g, 25.8 mmol) was added to a stirred suspension of 5-methyl-4-amino-thiophene-2-carboxylic acid hydrochloride (1.4 g, 7.0 mmol) in tetrahydrofuran (25 mL) under an inert atmosphere at room temperature. After 1-1/2 hours, phenylacetyl chloride (1.1 g, 7.2 mmol) was added. After 24 hours, the mixture was diluted with water (200 mL) and acidified with dilute aqueous hydrochloric acid. After 12 hours the precipitate was filtered off, rinsed with water, and dried to afford 1.5 g of 5-methyl-4-phenylacetyl amino-thiophene-2-carboxylic acid. Recrystallization of a sample from acetonitrile gave product with a mp 249-250°C.

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Step 2: 5-Methyl-4-phenylacetyl amino-thiophene-2-carboxylic acid benzylamide

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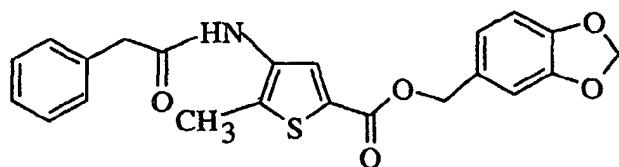
[0237] The title compound was prepared according to the procedure described for Example 2 using carbonyldimidazole (0.26 g, 1.7 mmol), 5-methyl-4-phenylacetyl amino-thiophene-2-carboxylic acid from Step 1 (0.29 g, 1.1 mmol), and benzyl amine (0.11 g, 1.1 mmol). Acidification of the aqueous workup mixture with dilute hydrochloric acid prior to filtration afforded 0.37 g of 5-methyl-4-phenylacetyl amino-thiophene-2-carboxylic acid benzylamide. A sample of the crude product was stirred in 2 M aqueous KHCO_3 for several hours, filtered off, rinsed with water, dried, and recrystallized from acetonitrile to give product with a mp 167-170°C.

EXAMPLE 11

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[0238]

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5-Methyl-4-phenylacetyl amino-thiophene-2-carboxylic acid 1,3-benzodioxol-5-ylmethyl ester

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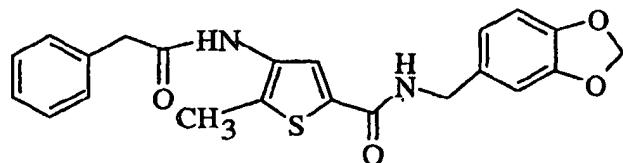
[0239] The title compound was prepared according to the procedure described for Example 2 using carbonyldimidazole (0.26 g, 1.7 mmol), 5-methyl-4-phenylacetyl amino-thiophene-2-carboxylic acid from Example 10, Step 1 (0.3 g, 1.1 mmol), and piperonyl alcohol (0.17 g, 1.1 mmol). Acidification of the aqueous workup mixture with dilute hydrochloric acid prior to filtration afforded 0.33 g of 5-methyl-4-phenylacetyl amino-thiophene-2-carboxylic acid 1,3-benzodioxol-5-ylmethyl ester. A sample of the product was stirred in 2 M aqueous KHCO_3 for several hours, filtered off, rinsed with water, and dried to give product with a mp 191-195°C.

EXAMPLE 12

[0240]

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5-Methyl-4-phenylacetylaminothiophene-2-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide

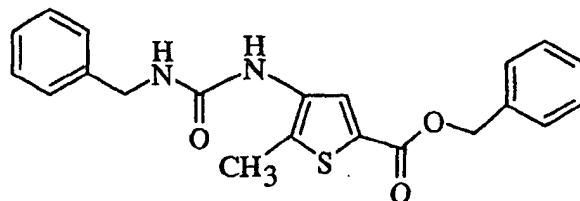
[0241] The title compound was prepared according to the procedure described for Example 2 using carbonyldiimidazole (0.26 g, 1.7 mmol), 5-methyl-4-phenylacetylaminothiophene-2-carboxylic acid from Example 10, Step 1 (0.3 g, 1.1 mmol), and piperonyl amine (0.17 g, 1.1 mmol) to afford 0.43 g of 5-methyl-4-phenylacetylaminothiophene-2-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide. A sample of the product was chromatographed on silica gel, eluting with ethyl acetate. Evaporation of the effluent under reduced pressure gave product with a mp 138-140°C.

20 EXAMPLE 13

[0242]

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4-(3-Benzyl-ureido)-5-methylthiophene-2-carboxylic acid benzyl ester

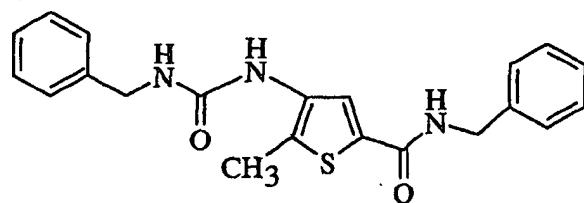
[0243] Benzyl isocyanate (0.29 g, 2.2 mmol) was added to a stirred solution of 5-methyl-4-aminothiophene-2-carboxylic acid benzyl ester from Example 9, Step 2 (0.5 g, 2.0 mmol) in toluene (10-15 mL) at room temperature under an inert atmosphere. After 20 minutes, the mixture was heated to reflux for 10 minutes, allowed to cool, then diluted with an equal volume of diethyl ether. After 10 minutes, the precipitate was filtered off, rinsed with ether, and dried to afford 0.5 g of 4-(3-benzyl-ureido)-5-methylthiophene-2-carboxylic acid benzyl ester; mp 208-209°C.

40 EXAMPLE 14

[0244]

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4-(3-Benzyl-ureido)-5-methylthiophene-2-carboxylic acid benzylamide Step 1: 5-Methyl-4-(3-benzyl-ureido)thiophene-2-carboxylic acid

[0245] A 2N aqueous potassium hydroxide solution (16 mL) was added to a stirred solution of 5-methyl-4-(3-benzyl-ureido)thiophene-2-carboxylic acid methyl ester from Step 2 of Example 16 below (0.4 g, 1.3 mmol) in warm methanol (4 mL), and the mixture was heated under reflux. After 1 hour the mixture was cooled, diluted with water (100 mL), and acidified with aqueous HCl. The precipitate was filtered off, rinsed with water, then ethanol, then ether, and dried to

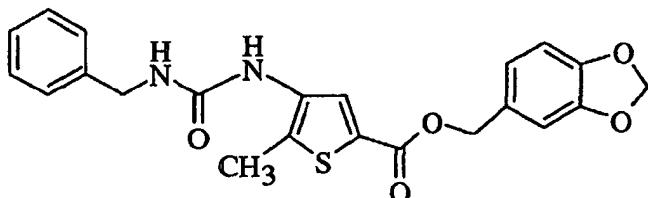
afford 0.29 g of 5-methyl-4-(3-benzyl-ureido)-thiophene-2-carboxylic acid; mp 259-260°C.

[0246] Step 2: 4-(3-Benzyl-ureido)-5-methyl-thiophene-2-carboxylic acid benzylamide

[0247] The title compound was prepared according to the procedure described for Example 2 using carbonyldimidazole (0.24 g, 1.7 mmol), 4-(3-benzyl-ureido)-5-methyl-thiophene-2-carboxylic acid from Step 3 (0.27 g, 0.9 mmol), and benzyl amine (0.1 g, 0.9 mmol) to afford 0.33 g of 4-(3-benzyl-ureido)-5-methylthiophene-2-carboxylic acid benzylamide. A sample of the crude product was stirred in 2 M aqueous KHCO_3 for several hours, filtered off, rinsed with water, dried, and recrystallized from methanol to give product with a mp 180-181°C.

EXAMPLE 15a

[0248]



4-(3-Benzyl-ureido)-5-methyl-thiophene-2-carboxylic acid 1,3-benzodioxol-5-ylmethyl ester

Step 1: 5-Methyl-4-nitro-thiophene-2-carboxylic acid 1,3-benzodioxol-5-ylmethyl ester

[0249] The title compound was prepared according to the procedure described for Example 2 using carbonyldimidazole (0.75 g, 4.3 mmol), 5-methyl-4-nitrothiophene-2-carboxylic acid (0.6 g, 3.2 mmol), and piperonyl alcohol (0.5 g, 3.3 mmol) to afford 0.8 g of 5-methyl-4-nitro-thiophene-2-carboxylic acid 1,3-benzodioxol-5-ylmethyl ester. A sample of the product was triturated in ethanol, cooled, filtered, and dried to give product with a mp 78-79°C.

Step 2: 5-Methyl-4-amino-thiophene-2-carboxylic acid 1,3-benzodioxol-5-ylmethyl ester

[0250] Sponge nickel (0.5 g water wet) was added to a solution of 5-methyl-4-nitro-thiophene-2-carboxylic acid 1,3-benzodioxol-5-ylmethyl ester (0.55 g, 1.7 mmol) from Step 1 in tetrahydrofuran (100 mL) and the mixture was hydrogenated at room temperature under a hydrogen atmosphere at a starting pressure of 50 psi. After a reaction time of 2.79 hours, the pressure was released, and the mixture was filtered. The slurry was washed with tetrahydrofuran, and the filtrate was stripped of solvent under reduced pressure to afford a crystalline residue. The residue was triturated in diethyl ether and filtered to afford 5-methyl-4-amino-thiophene-2-carboxylic acid 1,3-benzodioxol-5-ylmethyl ester. Chromatography on silica gel in ethyl acetate, then evaporation of the effluent under reduced pressure gave 0.14 g of 5-methyl-4-amino-thiophene-2-carboxylic acid 1,3-benzodioxol-5-ylmethyl ester.

Step 3: 4-(3-Benzyl-ureido)-5-methyl-thiophene-2-carboxylic acid 1,3-benzodioxol-5-ylmethyl ester

[0251] 5-Methyl-4-amino-thiophene-2-carboxylic acid 1,3-benzodioxol-5-ylmethyl ester from Step 2 (0.15 g, 0.5 mmol) was dissolved in hot 1,4-dioxane (6-8 mL) under an inert atmosphere, stirred, and treated with benzyl isocyanate (0.07 g, 0.5 mmol). After 72 hours at room temperature, the mixture was diluted with diethyl ether (50 mL). After another hour the precipitate was filtered off, rinsed with ether, and dried to afford 0.14 g of 4-(3-benzyl-ureido)-5-methyl-thiophene-2-carboxylic acid 1,3-benzodioxol-5-ylmethyl ester; mp 216-217°C.

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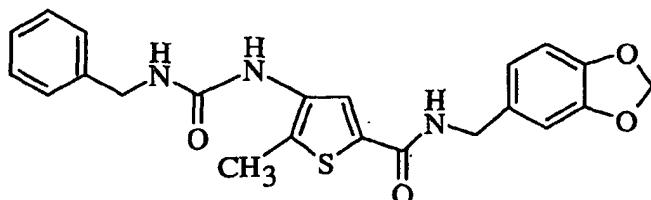
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EXAMPLE 15b

[0252]

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4-(3-Benzyl-ureido)-5-methyl-thiophene-2-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide

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Step 1: 5-Methyl-4-nitro-thiophene-2-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide

[0253] The title compound was prepared according to the procedure described for Example 2 using carbonyldimidazole (0.7 g, 4.3 mmol), 5-methyl-4-nitrothiophene-2-carboxylic acid (0.6 g, 3.2 mmol), and piperonyl amine (0.5 g, 3.3 mmol). Acidification of the aqueous workup mixture with dilute hydrochloric acid prior to filtration afforded 1 g of 5-methyl-4-nitro-thiophene-2-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide. A sample was dissolved in ethyl acetate and filtered through a short column of silica gel to give 5-methyl-4-nitrothiophene-2-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide; mp 181–183°C.

25 Step 2: 5-Methyl-4-amino-thiophene-2-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide

[0254] Sponge nickel (0.7 g water wet) was added to a solution of 5-methyl-4-nitro-thiophene-2-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide (0.72 g, 2.2 mmol) in methanol (50 mL), and the mixture was hydrogenated at room temperature under a hydrogen atmosphere at a starting pressure of 50 psi. After a reaction time of 1.77 hours, the pressure was released, and the mixture was filtered. The slurry was rinsed with methanol, and the filtrate was stripped of solvent under reduced pressure to afford 0.6 g of 5-methyl-4-amino-thiophene-2-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide as an oil.

35 Step 3: 4-(3-Benzyl-ureido)-5-methyl-thiophene-2-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide

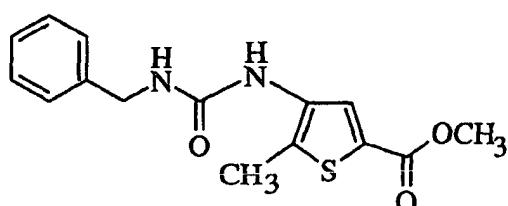
[0255] A mixture of 5-methyl-4-amino-thiophene-2-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide from Step 2 (0.6 g, 2.1 mmol) and benzyl isocyanate (0.28 g, 2.1 mmol) in 1,4-dioxane (100 mL) was stirred under an inert atmosphere and heated to reflux. After 30 minutes, the mixture was allowed to cool, and the solvent was removed under reduced pressure. The residue was triturated in a small amount of acetonitrile, cooled, and filtered to afford 0.33 g of 4-(3-benzyl-ureido)-5-methyl-thiophene-2-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide. A sample was recrystallized from methanol to give product with a mp 194–195°C.

EXAMPLE 16

45 [0256]

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5-Methyl-4-(3-benzyl-ureido)-thiophene-2-carboxylic acid methyl ester

Step 1: 5-Methyl-4-amino-thiophene-2-carboxylic acid methyl ester

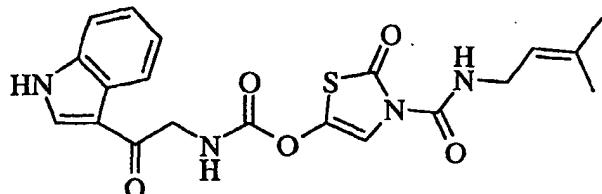
[0257] Sponge nickel (1.0 g water wet) was added to a solution of 5-methyl-4-nitro-thiophene-2-carboxylic acid methyl ester (1.79 g, 8.9 mmol) in methanol (50 mL), and the mixture was hydrogenated at room temperature under a hydrogen atmosphere at a starting pressure of 50 psi. After a reaction time of 25 hours, the pressure was released and the mixture filtered. The slurry was rinsed with methanol, and the filtrate was stripped of solvent under reduced pressure to afford 1.5 g of 5-methyl-4-amino-thiophene-2-carboxylic acid methyl ester. A sample was dissolved in ethyl acetate and filtered through a short column of silica gel. Evaporation of the effluent under reduced pressure gave product with a mp 90-91°C.

Step 2: 5-Methyl-4-(3-benzyl-ureido)-thiophene-2-carboxylic acid methyl ester

[0258] The title compound was prepared according to the procedure described for Example 13 using benzyl isocyanate (0.4 g, 3.2 mmol) and 5-methyl-4-aminothiophene-2-carboxylic acid methyl ester from Step 1 to afford 0.77 g of 5-methyl-4-(3-benzyl-ureido)-thiophene-2-carboxylic acid methyl ester. Recrystallization of a sample from acetonitrile gave product with a mp 185-187°C.

EXAMPLE 17

[0259]



[2-(1H-Indol-3-yl)-2-oxo-ethyl]-carbamic acid 3-(3-methyl-but-2-enylcarbamoyl)-2-oxo-2,3-dihydro-thiazol-5-yl ester

Step (a): Preparation of 3-(3-methyl-but-2-en-1-yl)aminocarbonyl-2,5-thiazolidinedione

[0260] To a stirred solution or partial solution of 2,5-thiazolidinedione (0.010 mol) in tetrahydrofuran (THF) is added neat (or a solution in dichloromethane or THF) (3-methyl-but-2-en-1-yl)-isocyanate (0.010 mol), prepared by allowing (3-methyl-but-2-en-1-yl)amine with 0.33 mol equivalents of triphosgene in dichloromethane optionally in the presence of a tertiary amine base or pyridine, and the mixture is stirred. Reaction progress may be followed by thin layer chromatography (TLC) or high performance liquid chromatography (HPLC). When a sufficient amount of desired product is formed, the mixture (or, optionally, the residue which is obtained after first rotary evaporating off the reaction solvent) is partitioned between ethyl acetate and an excess of about 0.1 M hydrochloric acid. The organic layer is washed with brine, dried over sodium sulfate, and rotary evaporated to give 3-(3-methyl-but-2-en-1-yl)aminocarbonyl-2,5-thiazolidinedione, which may be purified, if needed or desired, by chromatography on silica gel or crystallization.

Step (b): Preparation of 3-acetyl-1-(*tert*-butoxycarbonyl)-indole

[0261] To a stirred solution of 3-acetylindole (0.01 mol) in THF is added (BOC)₂O (0.01 mol) and a tertiary amine base (0.01 mol), and the mixture is stirred. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of desired product is formed, the mixture (or, optionally, the residue which is obtained after first rotary evaporating off the reaction solvent) is partitioned between ethyl acetate and an excess of about 0.1 M sodium hydroxide. The organic layer is washed with brine, dried over sodium sulfate, and rotary evaporated to give 3-acetyl-1-(*tert*-butoxycarbonyl)-indole, which may be purified, if needed or desired, by chromatography on silica gel or crystallization.

Step (c): Preparation of 3-bromoacetyl-1-(*tert*-butoxycarbonyl)-indole

[0262] To a stirred solution of 3-acetyl-1-(*tert*-butoxycarbonyl)-indole, which may be prepared as described in Step (b) above, (0.01 mol), in THF at a temperature of about -80°C to about 25°C is added bromine (0.01 mol), and the mixture is stirred from about 5 minutes to about 24 hours. Reaction progress may be followed by TLC or HPLC. When

a sufficient amount of desired product is formed, the mixture (or, optionally, the residue which is obtained after first rotary evaporating off the reaction solvent) is partitioned between ethyl acetate and an excess of an aqueous solution of sodium bisulfite or an aqueous solution of sodium thiosulfate. The organic layer is washed with water, then brine, dried over sodium sulfate, and rotary evaporated to give 3-bromoacetyl-1-(*tert*-butoxycarbonyl)-indole, which may be purified, if needed or desired, by chromatography on silica gel or crystallization.

5 Step (d): Preparation of 3-azidoacetyl-1-(*tert*-butoxycarbonyl)-indole

[0263] To a stirred solution of 3-bromoacetyl-1-(*tert*-butoxycarbonyl)-indole, which may be prepared as described in Step (c) above, (0.01 mol), in THF is added a solution or suspension of sodium azide (0.01 to 0.05 mol) in THF, which optionally contains from 0% to 50% water or methanol, and the mixture is stirred. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of desired product is formed, the mixture (or, optionally, the residue which is obtained after first rotary evaporating off the reaction solvent) is partitioned between ethyl acetate and water. The organic layer is washed with brine, dried over sodium sulfate, and rotary evaporated to give 3-azidoacetyl-1-(*tert*-butoxycarbonyl)-indole, which may be purified, if needed or desired, by chromatography on silica gel or crystallization.

10 Step (e): Preparation of 3-aminoacetyl-1-(*tert*-butoxycarbonyl)-indole

[0264] To a stirred solution of 3-azidoacetyl-1-(*tert*-butoxycarbonyl)-indole (0.01 mol), which may be prepared as described in Step (d) above, in THF is added a reducing agent such as, for example, a catalytic amount (0.0001 to 0.001 mol) of a hydrogenolysis catalyst such as, for example, 10% palladium on carbon, and the mixture is shaken under a hydrogen atmosphere at from atmospheric pressure to about 75 psi. (Alternatively, other reducing agents such as lithium aluminum hydride may be used. Reaction work-up conditions may be modified according to the reduction reaction employed.) Reaction progress may be followed by TLC or HPLC. When a sufficient amount of desired product is formed, the mixture is filtered, optionally through a filter aid such as, for example, CELITE (Celite Products Company, Los Angeles, California), and the filter cake is washed with additional solvent (THF). The filtrate and washings rotary evaporated to give 3-aminoacetyl-1-(*tert*-butoxycarbonyl)-indole, which may be purified, if needed or desired, by chromatography on silica gel or crystallization. Alternatively, the 3-aminoacetyl-1-(*tert*-butoxycarbonyl)-indole can be dissolved in ethyl ether, which optionally contains minor amounts (i.e., <50% v/v) of THF, and 1 mol equivalent of a solution of either hydrogen chloride in ethyl ether or concentrated hydrochloric acid is added. The solid 3-aminoacetyl-1-(*tert*-butoxycarbonyl)-indole hydrochloride which precipitates, or if little or no solid precipitates, the 3-aminoacetyl-1-(*tert*-butoxycarbonyl)-indole hydrochloride obtained upon rotary evaporation of the mixture, may be purified, if needed or desired, by crystallization. Step (f): Preparation of 2-(1-*tert*-butoxycarbonyl-indol-3-yl)-2-oxo-ethylisocyanate

[0265] To a stirred solution of 3-aminoacetyl-1-(*tert*-butoxycarbonyl)-indole, which may be prepared as described in Step (e) above, (0.01 mol), optionally in the presence of from 1 to 3 mol equivalents of a volatile (i.e., boiling point <150°C) non-nucleophilic base such as, for example, a volatile tertiary organic amine or pyridine, or a solid non-nucleophilic base such as, for example, sodium hydride, or 3-aminoacetyl-1-(*tert*-butoxycarbonyl)-indole hydrochloride, which may be prepared as described in Step (e) above, (0.01 mol), optionally in the presence of from 2 to 4 mol equivalents of said non-nucleophilic bases, in a solvent such as dichloromethane or ethyl acetate, is stirred. A suitable reagent such as, for example, 1 mol equivalent of phosgene or 0.33 mol equivalents of triphosgene is added. After stirring for from 10 minutes to about 24 hours, the mixture is diluted with up to an equal volume of a diluent such as diethyl ether or ethyl acetate (preferred diluent is diethyl ether), and any precipitates are filtered off. The filter cake is washed with additional diluent. The filtrate and washings are combined and rotary evaporated to give 2-(1-*tert*-butoxycarbonyl-indol-3-yl)-2-oxo-ethylisocyanate, which may be purified, if needed or desired, by vacuum distillation.

45 Step (g): Preparation of 2-[1-(*tert*-butoxycarbonyl)-indol-3-yl]-2-oxo-ethyl]carbamic acid, [3-(3-methyl-but-2-en-1-yl)aminocarbonyl-2,3-dihydrothiazol-2-on-5-yl] ester

[0266] To a stirred solution of 3-(3-methyl-but-2-en-1-yl)aminocarbonyl-2,4-thiazolidinedione (0.01 mol), which may be prepared as described in Step (a) above, in a solvent such as, for example, THF is added 1 mol equivalent of a non-nucleophilic base such as described in Step (f) above, preferably sodium hydride, and the mixture is stirred for from 1 minute to about 1 hour. To the mixture is added a solution of 2-(1-*tert*-butoxycarbonyl-indol-3-yl)-2-oxo-ethyl-isocyanate (0.01 mol), which may be prepared as described in Step (f) above, in a solvent such as, for example, THF. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of desired product is formed, the mixture is partitioned between ethyl acetate and water, or optionally the mixture is first rotary evaporated, and the residue is so partitioned. The organic layer is washed with 0.01 M hydrochloric acid, water, brine, and dried over sodium sulfate. The mixture is rotary evaporated to give 2-[1-(*tert*-butoxycarbonyl)-indol-3-yl]-2-oxo-ethyl]carbamic acid, [3-(3-methyl-but-2-en-1-yl)aminocarbonyl-2,3-dihydrothiazol-2-on-5-yl] ester, which may be purified, if needed or de-

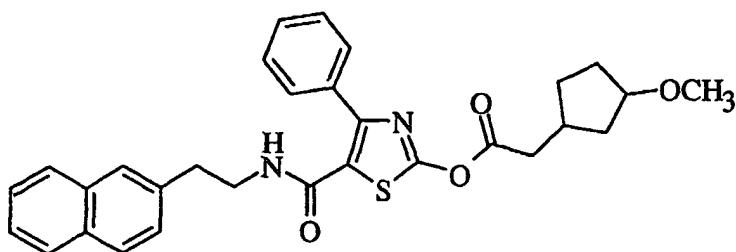
sired, by chromatography on silica gel or crystallization.

Step (h): Preparation of [2-(1H-indol-3-yl)-2-oxo-ethyl]-carbamic acid 3-(3-methyl-but-2-enylcarbamoyl)-2-oxo-2,3-dihydro-thiazol-5-yl ester

[0267] To a stirred solution of 2-[1-(*tert*-butoxycarbonyl)-indol-3-yl]-2-oxo-ethyl]carbamic acid, [3-(3-methyl-but-2-en-1-yl)aminocarbonyl-2,4-thiazolidinedion-5-yl] ester (0.01 mol), which may be prepared as described in Step (g) above, in dichloromethane or diethyl ether is added an excess of either hydrogen chloride gas or trifluoroacetic acid, and the mixture is stirred for from 1 minute to about 24 hours. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of desired product is formed, the mixture is partitioned between ethyl acetate and water, or optionally the mixture is first rotary evaporated, and the residue is so partitioned. The organic layer is washed with brine, dried over sodium sulfate, and rotary evaporated to give [2-(1H-indol-3-yl)-2-oxo-ethyl]-carbamic acid 3-(3-methyl-but-2-enylcarbamoyl)-2-oxo-2,3-dihydrothiazol-5-yl ester, which may be purified, if needed or desired, by chromatography on silica gel or crystallization.

EXAMPLE 18

[0268]



3-Methoxy-cyclopentylmethylcarboxylic acid 5-(2-naphthalen-2-yl-ethylcarbamoyl)-4-phenyl-thiazol-2-yl ester

Step (a): Preparation of thiocarbamic acid, benzyl ester

[0269] To a stirred solution of 1,1'-thiocarbonyldiimidazole (0.01 mol), in THF is added sodium benzyloxide (0.01 mol), and the mixture is stirred for from 1 minute to about 24 hours. To the mixture is added ammonia gas, and the mixture is stirred at atmospheric pressure or shaken at from atmospheric pressure to about 75 psi. Reaction progress may be followed by TLC or HPLC. (Alternatively, the imidazolyl leaving groups may be first activated (sequentially) by sulfonylation on nitrogen by pretreatment before each displacement with a suitable sulfonylating reagent such as trifluoromethanesulfonyl chloride or *para*-toluenesulfonyl chloride. This allows displacement of imidazolyl under less rigorous reaction conditions.) When a sufficient amount of desired product is formed, the mixture is partitioned between ethyl acetate and water, or optionally the mixture is first rotary evaporated, and the residue is so partitioned. The organic layer is washed with brine, dried over sodium sulfate, and rotary evaporated to give thiocarbamic acid, benzyl ester, which may be purified, if needed or desired, by chromatography on silica gel or crystallization.

Step (b): Preparation of 2-benzyloxy-4-phenyl-thiazol-5-carboxylic acid, ethyl ester

[0270] To a stirred solution of benzoylacetic acid, ethyl ester (0.01 mol) in a solvent such as, for example, chloroform is added N-bromosuccinimide (NBS, 0.01 mol), and the mixture is stirred. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of benzoyl-bromoacetic acid, ethyl ester is formed, ethyl acetate is added, and the mixture is rotary evaporated to remove chloroform. To the resulting ethyl acetate mixture is added thiocarbamic acid, benzyl ester, which may be prepared as described in Step (a) above, and a suitable non-nucleophilic base such as those described in Example 17 above, and the mixture is stirred. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of the desired product is formed, the reaction is washed with 0.01 M hydrochloric acid, water, brine, and dried over sodium sulfate. The mixture is rotary evaporated to give 2-benzyloxy-4-phenyl-thiazol-5-carboxylic acid, ethyl ester, which may be purified, if needed or desired, by chromatography on silica gel or crystallization.

Step (c): Preparation of 4-phenyl-thiazol-2-one-5-carboxylic acid, ethyl ester

[0271] To a stirred solution of 2-benzyloxy-4-phenyl-thiazol-5-carboxylic acid, ethyl ester (0.01 mol) in a solvent such as THF is added a suitable hydrogenation catalyst such as 10% palladium on carbon. The mixture is shaken under a

5 hydrogen atmosphere at a pressure of from atmospheric pressure to about 75 psi. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of the desired product is formed, the mixture is rotary evaporated to give 4-phenyl-thiazol-2-one-5-carboxylic acid, ethyl ester, which may be purified, if needed or desired, by chromatography on silica gel or crystallization. Alternatively, to a stirred solution of 2-benzyloxy-4-phenyl-thiazol-5-carboxylic acid, ethyl ester (0.01 mol) in a solvent such as dichloromethane is added a suitable ether-cleaving reagent such as boron tribromide, and the mixture is stirred. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of the

10 desired product is formed, the mixture is washed with 0.01 M sodium bicarbonate, water, brine, and dried over sodium sulfate. The mixture is rotary evaporated to give 4-phenyl-thiazol-2-one-5-carboxylic acid, ethyl ester, which may be purified, if needed or desired, by chromatography on silica gel or crystallization.

15 Step (d): Preparation of (\pm)-2-(3-methoxycyclopentylmethylcarboxy)-4-phenylthiazol-5-carboxylic acid, ethyl ester

[0272] To a stirred solution of give 4-phenyl-thiazol-2-one-5-carboxylic acid, ethyl ester (0.01 mol), which may be prepared as described above in Step (c), in a solvent such as THF is added a suitable non-nucleophilic base such as those described above in Example 17, followed by addition of (\pm)-3-methoxycyclopentylmethylcarbonyl chloride, and

20 the mixture is stirred. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of the desired product is formed, the mixture is partitioned between ethyl acetate and 0.01 M sodium bicarbonate. The organic layer is washed with water, brine, and dried over sodium sulfate. The mixture is rotary evaporated to give (\pm)-2-(3-methoxy-cyclopentylmethylcarboxy)-4-phenyl-thiazol-5-carboxylic acid, ethyl ester, which may be purified, if needed or desired, by chromatography on silica gel or crystallization.

25 Step (e): Preparation of (\pm)-2-(3-methoxycyclopentylmethylcarboxy)-4-phenylthiazol-5-carboxylic acid

[0273] To a stirred solution of (\pm)-2-(3-methoxycyclopentylmethylcarboxy)-4-phenyl-thiazol-5-carboxylic acid, ethyl ester (0.01 mol), which may be prepared as described in Step (d) above, in a solvent such as ethanol, aqueous ethanol,

30 or THF-ethanol, is added a solution of sodium or potassium hydroxide in ethanol at a concentration of from 1 M to about 2 M, and the mixture is stirred. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of the desired product is formed, the mixture is rotary evaporated to remove most of the organic solvents, and the concentrated mixture is washed with ethyl acetate. The aqueous layer is acidified with hydrochloric acid to a pH of about 2 to about 4, and the product which precipitates is filtered off to give (\pm)-2-(3-methoxycyclopentylmethylcarboxy)-4-phenyl-thiazol-5-carboxylic acid, which may be purified, if needed or desired, by chromatography on silica gel or crystallization.

Step (f): 3-Methoxy-cyclopentylmethylcarboxylic acid 5-(2-naphthalen-2-yl-ethylcarbamoyl)-4-phenyl-thiazol-2-yl ester

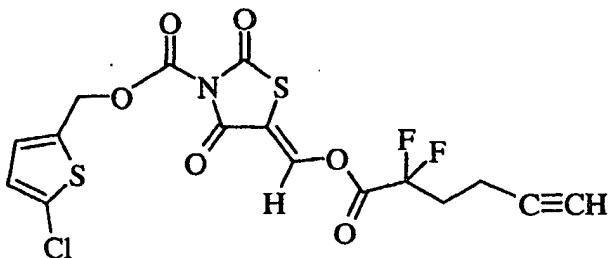
40 [0274] To a stirred solution of (\pm)-2-(3-methoxycyclopentylmethylcarboxy)-4-phenyl-thiazol-5-carboxylic acid (0.01 mol), which may be prepared as described above in Step (e), in a solvent such as THF is added 1,1'-carbonyldiimidazole, and the mixture is stirred from 10 minutes to about 24 hours. To this mixture is added naphth-2-ylethyl amine (0.01 mol), and the mixture is stirred. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of the desired product is formed, the mixture is rotary evaporated. The residue is partitioned between ethyl acetate and 0.01 M sodium hydroxide, and the organic layer is washed with water, brine, and dried over sodium sulfate. The mixture is rotary evaporated to give 3-methoxy-cyclopentylmethylcarboxylic acid 5-(2-naphthalen-2-yl-ethylcarbamoyl)-4-phenyl-thiazol-2-yl ester, which may be purified, if needed or desired, by chromatography on silica gel or crystallization. Alternatively, the (\pm)-2-(3-methoxycyclopentylmethylcarboxy)-4-phenyl-thiazol-5-carboxylic acid and naphth-2-ylethyl amine may be combined in a solvent such as THF and a coupling reagent such as dicyclohexylcarbodiimide (DCC) added to give the title compound. Alternatively, especially in the case where the starting carboxylic acid or amine is poorly soluble in nonpolar solvents such as THF, the reaction may be run in aqueous organic solvents using a water soluble carbodiimide coupling reagent.

EXAMPLE 19

[0275]

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[0276] *(E)*-5-(2,2-Difluoro-hex-5-ynoyloxymethylene)-2,4-dioxo-thiazolidine-3-carboxylic acid 5-chloro-thiophen-2-ylmethyl ester

Step (a): Preparation of 2,4-dimethoxythiazole

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[0277] To a stirred solution of 2,4-thiazolidindione (0.01 mol) in a solvent such as THF is added from 2 to 4 mol equivalents of a non-nucleophilic base such as sodium hydride or LDA, followed by methyl iodide, and the mixture is stirred. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of the desired product is formed, the mixture is partitioned between ethyl acetate and water. The organic layer is washed with brine, dried over sodium sulfate, and rotary evaporated to give 2,4-dimethoxythiazole, which may be purified, if needed or desired, by chromatography on silica gel or crystallization.

Step (b): Preparation of 2,4-dimethoxythiazole-5-carboxaldehyde

[0278] To a stirred solution of 2,4-dimethoxythiazole (0.01 mol), which may be prepared as described in Step (a) above, in dichloromethane is added N-phenyl-N-methylformamide (0.01 mol) and phosphorous oxychloride (POCl_3 , 0.01 mol), or optionally phosgene or trifluoromethanesulfonic acid anhydride instead of POCl_3 , and the mixture is stirred. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of the desired product is formed, the mixture is partitioned between ethyl acetate and water. The organic layer is washed with brine, dried over sodium sulfate, and rotary evaporated to give 2,4-dimethoxythiazole-5-carboxaldehyde, which may be purified, if needed or desired, by chromatography on silica gel or crystallization.

Step (c): Preparation of *(E)*-5-(2,2-difluoro-hex-5-ynoyloxymethylene)-2-methoxy-4,5-dihydro-thiazolin-4-one

[0279] To a stirred solution of 2,4-dimethoxythiazole-5-carboxaldehyde (0.01 mol), which may be prepared as described in Step (b) above, in a solvent such as dichloromethane is added phosphorous tribromide or another suitable ether cleaving reagent, and the mixture is stirred. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of the corresponding 2,4-thiazolidindione-5-carboxaldehyde is formed, the reaction is partitioned between ethyl acetate and water. The organic layer is washed with brine, dried over sodium sulfate, and rotary evaporated. The residue is dissolved in THF, and 1 mol equivalent of a suitable non-nucleophilic base as described above in Example 17 is added, followed by 1 mol equivalent of methyl iodide. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of the corresponding 2-methoxy-4,5-dihydro-thiazolin-4-one-5-carboxaldehyde is formed, the mixture is partitioned and worked up as described above. The resulting residue is dissolved in THF, and 1 mol equivalent of a suitable non-nucleophilic base as described above in Example 17 is added, followed by 1 mol equivalent of 2,2-difluoro-hex-5-ynoyl chloride, and the mixture is stirred. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of the desired product is formed, the reaction is partitioned and worked up as described above to give *(E)*-5-(2,2-difluoro-hex-5-ynoyloxymethylene)-2-methoxy-4,5-dihydro-thiazolin-4-one, which may be purified, if needed or desired, by chromatography on silica gel or crystallization. Also formed is *(Z)*-5-(2,2-difluoro-hex-5-ynoyloxymethylene)-2-methoxy-4,5-dihydro-thiazolin-4-one, which may be purified, if needed or desired, by chromatography on silica gel or crystallization.

Step (d): Preparation of (*E*)-5-(2,2-difluoro-hex-5-ynoyloxymethylene)-2,4-thiazolidindione

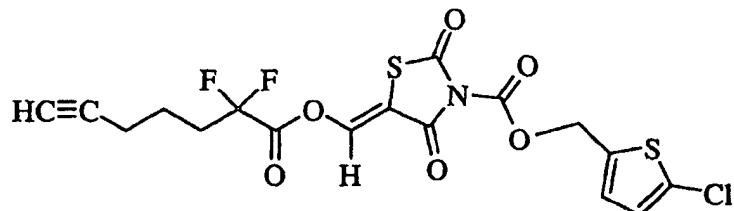
[0280] To a stirred solution of (*E*)-5-(2,2-difluoro-hex-5-ynoyloxymethylene)-2-methoxy-4,5-dihydro-thiazolin-4-one (0.01 mol), which may be prepared as described in Step (c) above, in dichloromethane is added phosphorous tribromide or another suitable ether cleaving reagent, and the mixture is stirred. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of the desired product is formed, the reaction is partitioned and worked up as described in Step (c) above to give (*E*)-5-(2,2-difluoro-hex-5-ynoyloxymethylene)-2,4-thiazolidindione, which may be purified, if needed or desired, by chromatography on silica gel or crystallization.

5 10 Step (e): Preparation of (*E*)-5-(2,2-difluoro-hex-5-ynoyloxymethylene)-2,4-dioxothiazolidine-3-carboxylic acid 5-chloro-thiophen-2-ylmethyl ester

[0281] To a stirred solution of (*E*)-5-(2,2-difluoro-hex-5-ynoyloxymethylidene)-2,4-thiazolidindione, which may be prepared as described in Step (d) above, in THF is added 2 mol equivalents of a non-nucleophilic base such as one of those described above in Example 17, followed by 1 mol equivalent of phosgene or 0.33 mol equivalents of triphosgene, and the mixture is stirred. After stirring for from 1 minute to about 1 hour, 5-chlorothiophen-2-ylmethyl alcohol is added, and the mixture is stirred. Reaction progress may be followed by TLC or HPLC. When a sufficient amount of the desired product is formed, the reaction is partitioned between ethyl acetate and water. The organic layer is washed with 0.01 M sodium bicarbonate, water, brine, and dried over sodium sulfate. The mixture is rotary evaporated to give (*E*)-5-(2,2-difluoro-hex-5-ynoyloxymethylene)-2,4-dioxo-thiazolidine-3-carboxylic acid 5-chloro-thiophen-2-ylmethyl ester, which may be purified, if needed or desired, by chromatography on silica gel or crystallization.

EXAMPLE 20

25 [0282]

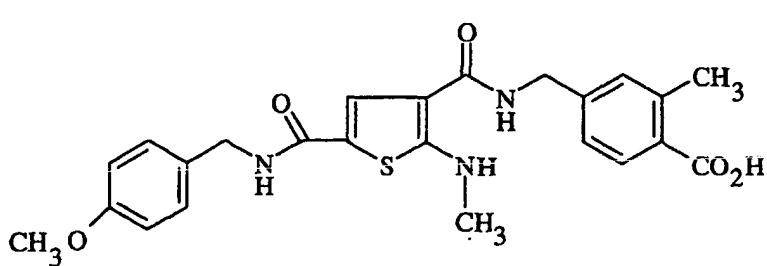


(*Z*)-5-(2,2-Difluoro-hex-5-ynoyloxymethylene)-2,4-dioxo-thiazolidine-3-carboxylic acid 5-chloro-thiophen-2-ylmethyl ester

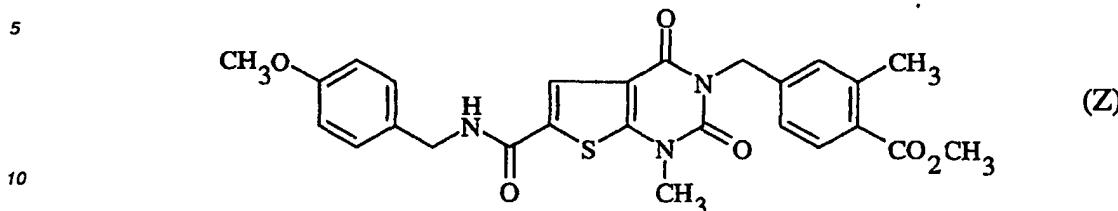
[0283] In a manner similar to Example 19, Steps (d) and (e), (*Z*)-5-(2,2-difluorohex-5-ynoyloxymethylene)-2-methoxy-4,5-dihydro-thiazolin-4-one, prepared according to the procedure described above in Example 19, Step (c), is converted to (*Z*)-5-(2,2-difluoro-hex-5-ynoyloxymethylene)-2,4-dioxo-thiazolidine-3-carboxylic acid 5-chloro-thiophen-2-ylmethyl ester, which may be purified, if needed or desired, by chromatograph on silica gel or crystallization.

EXAMPLE 21

45 [0284]



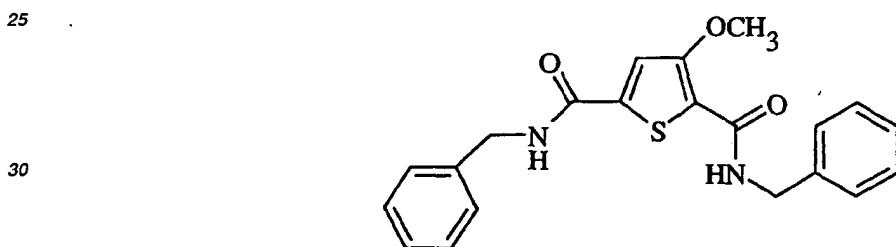
4-({[5-(4-Methoxy-benzylcarbamoyl)-2-methylamino-thiophene-3-carbonyl]-amino}-methyl)-2-methyl-benzoic acid
 [0285] An amount (0.0863 g, 0.000170 mol) of the compound of Formula (Z)



15 and potassium carbonate (0.0773 g, 0.000559 mol) in a mixture of water (3 mL) and methanol (3 mL) was heated to reflux under nitrogen for 24 hours. After cooling to room temperature, the mixture was acidified with concentrated hydrochloric acid. A solid was filtered off and dried in vacuo to yield 0.078 g of 4-({[5-(4-methoxy-benzylcarbamoyl)-2-methylamino-thiophene-3-carbonyl]-amino}-methyl)-2-methyl-benzoic acid as a white powder; MS-APCI⁺ (M+1): 468.2; Elem. Anal. Calc'd for C₂₄H₂₅N₃O₅S·1.17 H₂O: C, 58.99; H, 5.64; N, 8.60; S, 6.56. Found: C, 58.61; H, 5.44; N, 8.52; S, 6.87.

20 EXAMPLE 22

[0286]



35 3-Methoxy-thiophene-2,5-dicarboxylic acid bis benzylamide

[0287] A mixture of 3-methoxy-thiophene-2,5-dicarboxylic acid (0.382 g), benzylamine (0.41 mL), N,N'-carboxyl-diimidazole (0.66 g), and DMF was heated at 60°C to yield 0.39 g of 3-methoxy-thiophene-2,5-dicarboxylic acid bis benzylamide; MI-APCI⁺ 381.1; Elem. Anal. (C₂₁H₂₀N₂O₃S); Calc'd: C, 66.30; H, 5.30; N, 7.36. Found: C, 66.52; H, 5.06; N, 7.41.

40 EXAMPLE 23

[0288] 5-(3-Benzyl-ureido)-1,3,4-thiadiazole-2-carboxylic acid benzyl ester

45 Step (a): Acrylic acid benzyl ester

[0289] To a solution of benzyl alcohol (4.76 mL, 0.046 mol), 4-dimethylaminopyridine ("DMAP," 0.790 g, 0.0065 mol) and triethylamine (12.85 mL, 0.09297 mol) in dichloromethane (92 mL) was added a solution of acryloyl chloride (7.54 mL, 0.09297 mol) slowly at 0°C, and the mixture was stirred at 0°C for 2.5 hours. The mixture was quenched with aqueous sodium bicarbonate, and the quenched mixture was extracted with dichloromethane (2 × 100 mL). The extracts were combined, dried (MgSO₄), and rotary evaporated to give a yellow oil. The oil was purified by column chromatography, eluting with hexanes/ethyl acetate (95:5) to give 5.19 g (64%) of acrylic acid benzyl ester as a clear oil.

55 Step (b): Benzyl glyoxalate

[0290] To a clear solution of the product of Step (a) (1 g, 0.006 mol) in water and dioxane was added osmium tetroxide (0.0216 g, 0.0000851 mol). After 5 minutes the clear solution had turned dark brown. Sodium periodate (2.43 g, 0.0114 mol) was added portionwise over 0.5 hour, and the mixture was stirred for 3 hours. The resulting cream-colored sus-

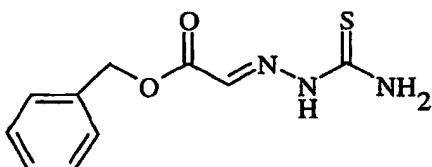
pension was filter d. The filtrate was extracted with ethyl ether (3 × 50 mL). The extracts were combined, dried (MgSO_4), and rotary vaporated to give a dark brown oil; yield 0.92 g (99%), which was benzyl glyoxalate.

Step (c):

5

[0291]

10



15

[0292] To a solution of acetic acid was added N-aminothiourea (0.555 g), and the mixture was heated at 80°C until the yellow mixture became homogeneous. The temperature was lowered to 50°C, and the product of Step (b) (1 g, 0.006 mol) was added dropwise. After addition was complete, the heat was turned off, and the mixture stirred overnight at room temperature. After 24 hours, the mixture was filtered, and the filtercake was washed with acetic acid (5 mL), then cold water (2 × 5 mL). The resulting cream-colored filtercake was the Step (c) title compound according to $^1\text{H-NMR}$ and MS; yield 0.8 g (55%).

20

Step (d): 5-Amino-1,3,4-thiadiazole-2-carboxylic acid benzyl ester

25

[0293] To a solution of acetic acid was added the product of Step (c) (0.1 g, 0.00042 mol) followed by a solution of iron (III) chloride in water, after dissolving the iron (III) chloride completely in water at 50°C. The mixture was stirred at room temperature for 1 hour, then ice and water were added, and the mixture was stirred vigorously. After 5 minutes, the mixture was filtered to give a white powder. Additional solids were obtained by concentrating the filtrate and diluting the concentrated filtrate with water. Total yield 0.05 g of 5-amino-1,3,4-thiadiazole-2-carboxylic acid benzyl ester; mp 198-200°C.

30

Step (e): 5-(3-Benzyl-ureido)-1,3,4-thiadiazole-2-carboxylic acid benzyl ester

35

[0294] To a solution of the product of Step (d) (0.1 g, 0.000425 mol) in THF (6.07 mL) was added benzyl isocyanate (0.0525 mL, 0.000425 mol), and the mixture was stirred overnight at room temperature. After 24 hours, the mixture was rotary evaporated and the concentrate was diluted with ethyl ether and dichloromethane. A solid was filtered and washed with ethyl ether. The mother filtrate was rotary evaporated and the residue triturated with ethyl ether and dichloromethane to give additional solids. The solids were combined to give 0.12 g of 5-(3-benzyl-ureido)-1,3,4-thiadiazole-2-carboxylic acid benzyl ester; mp 188-192°C.

40

[0295] The invention compounds of Formula I have been evaluated in standard assays for their ability to inhibit the activity of various MMP enzymes. The assays used to evaluate the biological activity of the invention compounds are well known and routinely used by those skilled in the study of MMP inhibitors and their use to treat clinical conditions.

45

[0296] The assays measure the amount by which a test compound inhibits the hydrolysis of a thiopeptolide substrate caused by a matrix metalloproteinase enzyme. Such assays are described in detail by Ye et al., in *Biochemistry*, 1992; 31(45):11231-11235, which is incorporated herein by reference.

50

[0297] Thiopeptolide substrates show virtually no decomposition or hydrolysis in the absence of a matrix metalloproteinase enzyme. A typical thiopeptolide substrate commonly utilized for assays is Ac-Pro-Leu-Gly-thioester-L-Leu-Leu-Gly-OEt. A 100 μL assay mixture will contain 50 mM of 2-morpholinoethane sulfonic acid monohydrate (MES, pH 6.0) 10 mM CaCl_2 , 100 μM thiopeptolide substrate, and 1 mM 5,5'-dithio-bis-(2-nitro-benzoic acid) (DTNB). The thiopeptolide substrate concentration is varied from 10 to 800 μM to obtain K_m and K_{cat} values. The change in absorbance at 405 nm is monitored on a Thermo Max microplate reader (Molecular Devices, Menlo Park, CA) at room temperature (22°C). The calculation of the amount of hydrolysis of the thiopeptolide substrate is based on $E_{412} = 13600 \text{ m}^{-1} \text{ cm}^{-1}$ for the DTNB-derived product 3-carboxy-4-nitrothiophenoxide. Assays are carried out with and without matrix metalloproteinase inhibitor compounds, and the amount of hydrolysis is compared for a determination of inhibitory activity of the test compounds.

55

[0298] Several representative compounds have been evaluated for their ability to inhibit various matrix metalloproteinase enzymes. The invention compounds are uniquely active in inhibiting MMP-13. Table 1 below presents inhibitory activity for invention compounds in the column labelled "MMP-13CD IC_{50} , μM ". In the table, MMP-13CD refers to the

catalytic domain of collagenase-3. It has been shown previously (Ye Qi-Zhuang, Hupe D., Johnson L., *Current Medicinal Chemistry*, 1996;3:407-418) that inhibitor activity against a catalytic domain of an MMP is predictive of the inhibitor activity against the respective full-length enzyme. Test compounds were evaluated at various concentrations in order to determine their respective IC₅₀ values, the micromolar concentration of compound required to cause a 50% inhibition of the hydrolytic activity of the respective enzyme.

Table 1

	Compound of Example No.	MMP-13CD IC ₅₀ , μ M
10	1	8.6
	2	0.85
	3	3.6
	4	0.20
	5	0.45
15	6	0.37
	7	0.97
	8	3.0
	9	2.3
	10	30
20	11	0.19
	12	2.7
	13	22
	14	14
	15b	0.92
25	16	2
	21	3.4
	22	≥100
	23	30
30		

[0299] The foregoing data in Table 1 establish that the invention compounds are potent inhibitors of MMP-13.

[0300] The invention compounds are also selective inhibitors of MMP-13 versus other MMP enzymes, including versus MMP-7 and MMP-9. This is shown by comparing the IC₅₀ data presented below in Table 2 in the columns labeled "MMP-7 IC₅₀ (μ M)," "MMP-9CD IC₅₀ (μ M)," and "MMP-13CD IC₅₀ (μ M)," respectively.

Table 2

	Compound of Example No.	MMP-7IC ₅₀ (μ M)	MMP-9CD IC ₅₀ (μ M)	MMP-13CD IC ₅₀ (μ M)
40	1	100	100	8.6
	2	30	30	0.85
	3	100	100	3.6
	4	30	100	0.20
	5	10	30	0.45
45	6	32	100	0.37
	7	100	100	0.97
	8	100	100	3.0
	9	100	100	2.3
	10	100	30	30
50	11	100	100	0.19
	12	100	100	2.7
	13	30	30	22
	14	100	99	14
	15a	N/A ^a	N/A	0.35
55	15b	45	30	0.92

^a N/A means datum not available.

Table 2 (continued)

Compound of Exampl No.	MMP-7IC ₅₀ (μM)	MMP-9CD IC ₅₀ (μM)	MMP-13CD IC ₅₀ (μM)
16	100	100	2

5 [0301] The foregoing data establish that the invention compounds of Formula I are potent inhibitors of MMP enzymes, and are especially useful due to their selective inhibition of MMP-13. Because of this potent and selective inhibitory activity, the invention compounds are especially useful to treat diseases mediated by the MMP enzymes, and particularly those mediated by MMP-13.

10 [0302] The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I. The active compound generally is present in a concentration of about 5% to about 95% by weight of the formulation.

15 [0303] For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

20 [0304] In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

25 [0305] In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

30 [0306] The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier

35 [0307] providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

40 [0308] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

45 [0309] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

50 [0310] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

55 [0311] Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

60 [0312] The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

65 [0313] The quantity of active component in a unit dose preparation may be varied or adjusted from 1 mg to 1000 mg, preferably 10 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

70 [0314] In therapeutic use as agents to inhibit a matrix metalloproteinase enzyme for the treatment of atherosclerotic plaque rupture, aortic aneurism, heart failure, restenosis, periodontal disease, corneal ulceration, cancer metastasis,

tumor angiogenesis, arthritis, or other autoimmune or inflammatory disorders dependent upon MMP-mediated breakdown of connective tissue, the compounds utilized in the pharmaceutical method of this invention are administered at a dose that is effective to inhibit the hydrolytic activity of one or more matrix metalloproteinase enzymes. The initial dosage of about 1 mg to about 100 mg per kilogram daily will be effective. A daily dose range of about 25 mg to about 5

75 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered 10 in portions during the day if desired. Typical dosages will be from about 0.1 to about 500 mg/kg, and ideally about 25 to about 250 mg/kg, such that it will be an amount which is effective to treat the particular disease being prevented or controlled.

[0315] The following examples illustrate pharmaceutical compositions of the present invention. The examples are representative only, and are not to be construed as limiting the invention in any respect.

15 FORMULATION EXAMPLE 1

[0316]

20

Tablet Formulation:	
Ingredient	Amount (mg)
The compound of Example 1	25
Lactose	50
Cornstarch (for mix)	10
Cornstarch (paste)	10
Magnesium stearate (1%)	5
Total	100

25 [0317] The compound of Example 1, lactose, and cornstarch (for mix) are blended to uniformity. The cornstarch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet. Such tablets can be administered to a human 30 from one to four times a day for treatment of disease caused by overactivity of matrix metalloproteinases.

35 FORMULATION EXAMPLE 2

40 Coated Tablets:

[0318] The tablets of Formulation Example 1 are coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth, and colorant.

45 FORMULATION EXAMPLE 3

50 Injection vials:

[0319] The pH of a solution of 500 g of the compound of Example 4 and 5 g of disodium hydrogen phosphate is adjusted to pH 6.5 in 3 L of double-distilled water using 2 M hydrochloric acid. The solution is sterile filtered, and the 55 filtrate is filled into injection vials, lyophilized under sterile conditions, and aseptically sealed. Each injection vial contains 25 mg of the compound of Example 4.

FORMULATION EXAMPLE 4

55 Suppositories:

[0320] A mixture of 25 g of the compound of Example 6, 100 g of soya lecithin, and 1400 g of cocoa butter is fused, poured into molds, and allowed to cool. Each suppository contains 25 mg of the compound of Example 6.

FORMULATION EXAMPLE 5

Solution:

5 [0321] A solution is prepared from 1 g of the compound of Example 5, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 12\text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$, and 0.1 g benzalkonium chloride in 940 mL of double-distilled water. The pH of the solution is adjusted to pH 6.8 using 2 M hydrochloric acid. The solution is diluted to 1.0 L with double-distilled water, and sterilized by irradiation. A 25 mL volume of the solution contains 25 mg of the compound of Example 5.

10 FORMULATION EXAMPLE 6

Ointment:

15 [0322] 500 mg of the compound of Example 2 is mixed with 99.5 g of petroleum jelly under aseptic conditions. A 5 g portion of the ointment contains 25 mg of the compound of Example 2.

FORMULATION EXAMPLE 7

Capsules:

20 [0323] 2 kg of the compound of Example 3 are filled into hard gelatin capsules in a customary manner such that each capsule contains 25 mg of the invention compound.

FORMULATION EXAMPLE 8

Ampoules:

25 [0324] A solution of 2.5 kg of the compound of Example 8 is dissolved in 60 L of double-distilled water. The solution is sterile filtered, and the filtrate is filled into ampoules. The ampoules are lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 25 mg of the compound of Example 8.

30 [0325] Having described the present invention above, certain embodiments of the present invention are hereupon claimed.

35 **Claims**

1. A compound of Formula I

40 $\text{G}_1-(\text{C}(\text{R}_1)\text{R}_2)_n-\text{Q}_1-\text{B}-\text{Q}_2-(\text{C}(\text{R}_3)\text{R}_4)_m-\text{G}_2$

1

45 or a pharmaceutically acceptable salt thereof;
wherein:

50 G_1 and G_2 are independently selected from:

hydrogen,
 $\text{C}_1\text{-C}_{12}$ alkyl,
 substituted $\text{C}_1\text{-C}_{12}$ alkyl,
 $\text{C}_2\text{-C}_{12}$ alkenyl,
 substituted $\text{C}_2\text{-C}_{12}$ alkenyl,
 $\text{C}_2\text{-C}_{12}$ alkynyl,
 substituted $\text{C}_2\text{-C}_{12}$ alkynyl,
 $\text{C}_3\text{-C}_{12}$ cycloalkyl,
 substituted $\text{C}_3\text{-C}_{12}$ cycloalkyl,
 phenyl,
 substituted phenyl,

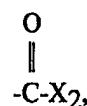
5 naphthyl,
substituted naphthyl,
heteroaryl, and
substituted heteroaryl;

10 R₁, R₂, R₃, and R₄ are independently, at each occurrence, selected from:

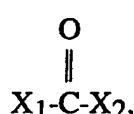
15 hydrogen,
methyl,
cyano, and
fluoro, or R₁ and R₂, or R₃ and R₄, may be taken together with the carbon atom to which they are each attached to form C=O;

20 n and m are independently an integer of from 1 to 3;

25 Q₁ is



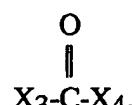
40 , or



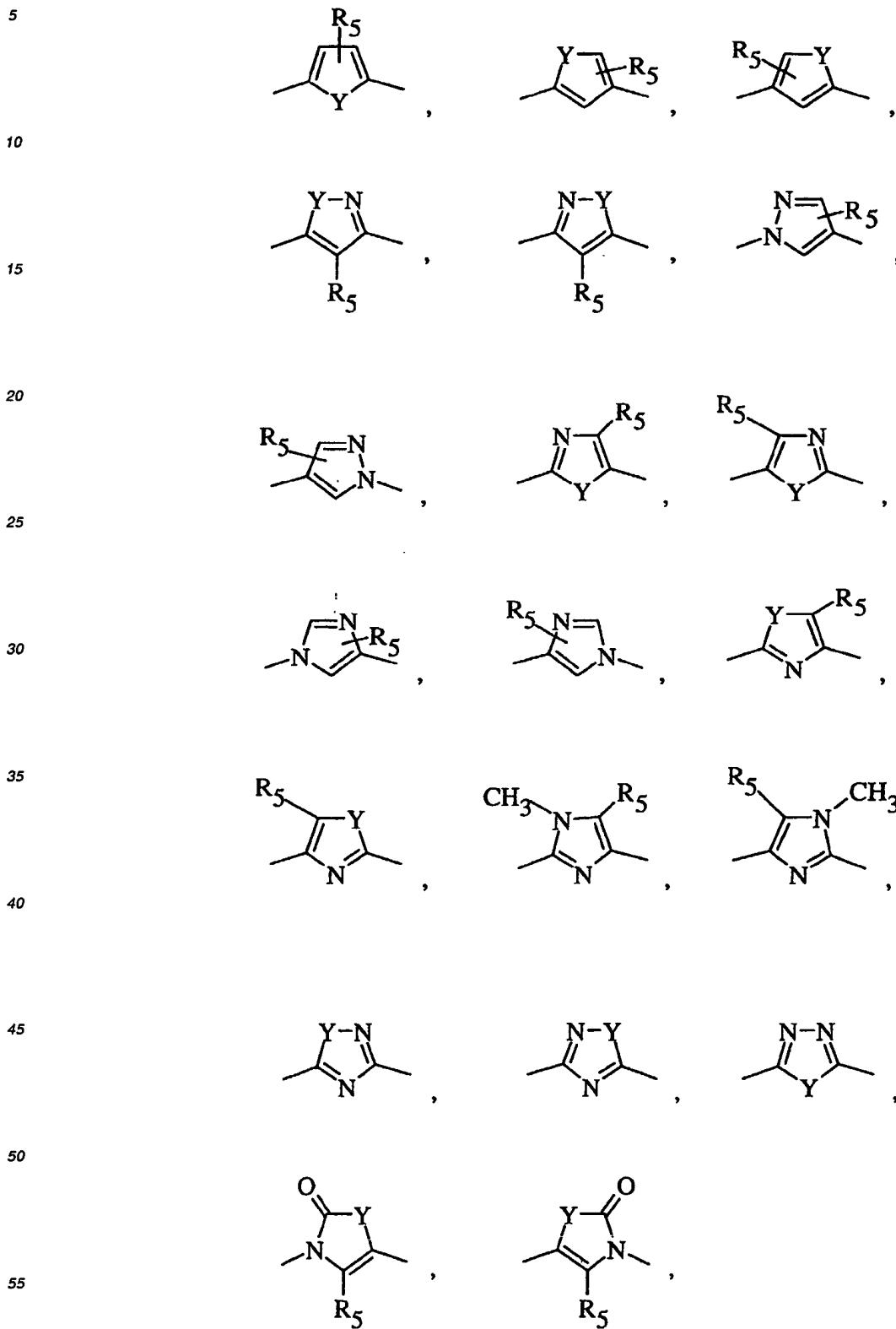
50 wherein X₁ and X₂ are independently O or N(H);
Q₂ is



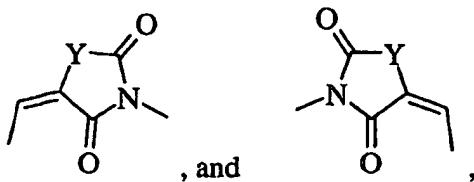
50 or



wherein X_3 and X_4 are independently O or N(H); and B is a 5-membered heterocyclene selected from:

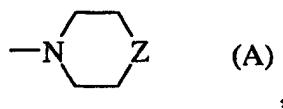


5



10 wherein Y is O, S, or N-CH₃, and
R₅ is selected from:

15 hydrogen,
C₁-C₁₂ alkyl,
substituted C₁-C₁₂ alkyl,
C₂-C₁₂ alkenyl,
substituted C₂-C₁₂ alkenyl,
C₂-C₁₂ alkynyl,
20 substituted C₂-C₁₂ alkynyl,
C₃-C₁₂ cycloalkyl,
substituted C₃-C₁₂ cycloalkyl,
phenyl,
substituted phenyl,
benzyl,
25 substituted benzyl,
O-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
S-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
C(O)-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
30 CO₂R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
C(O)-N(H)OR₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
C(=NOR₆)-H, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
C(=NOR₆)-CH₃, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
35 CH₂OR₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
CH₂N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and
R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated
40 heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic
ring of formula (A)



45 wherein Z is CH₂, O, S, or N-R, wherein R is H or CH₃,
C(H)F-OH,
CF₂-OH,
O-C(O)-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
50 C(O)-N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and
R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated
heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic
ring of formula (A), wherein (A) is as defined above,
55 N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇
are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated
heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic
ring of formula (A), wherein (A) is as defined above,
N(R₆)-C(O)-R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
N(H)-C(O)-N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or

R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

5 $N(H)-C(O)-OR_6$, wherein R_6 is independently hydrogen, C_1-C_{12} alkyl, phenyl, or benzyl,

$N(H)-S(O)_2-(C_1-C_{12}$ alkyl),

$O-C(O)-N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1-C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

10 NO_2 ,

N_3 ,

$N(H)-C(NR_8)-N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1-C_4 alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above, and R_8 is hydrogen, hydroxy, methoxy, or CN,

15 CN ,

halo,

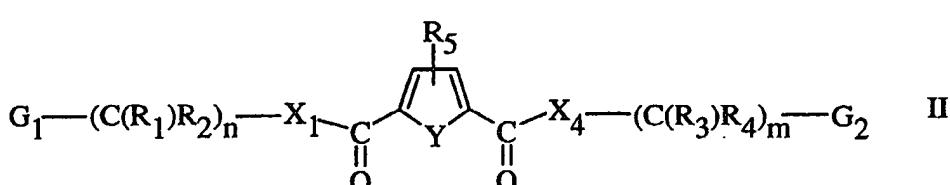
$S(O)-(C_1-C_{12}$ alkyl),

$S(O)_2-(C_1-C_{12}$ alkyl),

20 $S(O)_2-N(R_6)-(R_7)$, wherein R_6 and R_7 are independently hydrogen, C_1-C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above, and

25 $S(O)_2CF_3$, wherein at least one of R_1 , R_2 , R_3 , R_4 , or R_5 is not hydrogen, or at least one of G_1 or G_2 is substituted C_1-C_{12} alkyl, substituted C_2-C_{12} alkenyl, substituted C_2-C_{12} alkynyl, substituted C_3-C_{12} cycloalkyl, substituted phenyl, substituted naphthyl, or substituted heteroaryl.

2. The compound according to Claim 1 of Formula II



or a pharmaceutically acceptable salt thereof;

wherein:

40 Y is O, S, or $N-CH_3$;

X_1 and X_4 are each independently O or NH;

G_1 and G_2 are independently selected from:

45 hydrogen,

C_1-C_{12} alkyl,

substituted C_1-C_{12} alkyl,

C_2-C_{12} alkenyl,

substituted C_2-C_{12} alkenyl,

C_2-C_{12} alkynyl,

substituted C_2-C_{12} alkynyl,

C_3-C_{12} cycloalkyl,

substituted C_3-C_{12} cycloalkyl,

phenyl,

substituted phenyl,

naphthyl,

substituted naphthyl,

heteroaryl, and

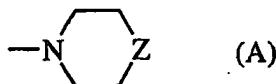
substituted heteroaryl;

R_1, R_2, R_3 , and R_4 are independently, at each occurrence, selected from:

5 hydrogen,
methyl,
cyano, and
fluoro, or R_1 and R_2 , or R_3 and R_4 , may be taken together with the carbon atom to which they are each attached to form $C=O$; and

B- is selected from:

15	hydrogen, C ₁ -C ₁₂ alkyl, substituted C ₁ -C ₁₂ alkyl, C ₂ -C ₁₂ alkenyl, substituted C ₂ -C ₁₂ alkenyl, C ₂ -C ₁₂ alkynyl, substituted C ₂ -C ₁₂ alkynyl,
20	C ₃ -C ₁₂ cycloalkyl, substituted C ₃ -C ₁₂ cycloalkyl, phenyl, substituted phenyl, benzyl, substituted benzyl,
25	O-R ₆ , wherein R ₆ is hydrogen, C ₁ -C ₁₂ alkyl, phenyl, or benzyl, S-R ₆ , wherein R ₆ is hydrogen, C ₁ -C ₁₂ alkyl, phenyl, or benzyl, C(O)-R ₆ , wherein R ₆ is hydrogen, C ₁ -C ₁₂ alkyl, phenyl, or benzyl, CO ₂ R ₆ , wherein R ₆ is hydrogen, C ₁ -C ₁₂ alkyl, phenyl, or benzyl, C(O)-N(H)OH,
30	C(=NOR ₆)-H, wherein R ₆ is hydrogen, C ₁ -C ₁₂ alkyl, phenyl, or benzyl, C(=NOR ₆)-CH ₃ , wherein R ₆ is hydrogen, C ₁ -C ₁₂ alkyl, phenyl, or benzyl, CH ₂ OR ₆ , wherein R ₆ is hydrogen, C ₁ -C ₁₂ alkyl, phenyl, or benzyl, CH ₂ N(R ₆)R ₇ , wherein R ₆ and R ₇ are independently hydrogen, C ₁ -C ₁₂ alkyl, phenyl, or benzyl, or R ₆ and R ₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A)
35	



45 wherein Z is CH_2 , O, S, or N-R, wherein R is H or CH_3 ,

50 C(H)F-OH,
 CF₂-OH,
 O-C(O)-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 C(O)-N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,
 N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,
 55 N(R₆)-C(O)-R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 N(H)-C(O)-N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or

R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

5 $N(H)-C(O)-OR_6$, wherein R_6 is independently hydrogen, C_1-C_{12} alkyl, phenyl, or benzyl, $N(H)-S(O)_2-(C_1-C_{12}$ alkyl),

$O-C(O)-N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1-C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

10 NO_2 ,

N_3 ,

$N(H)-C(NR_8)-N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1-C_4 alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above, and R_8 is hydrogen, hydroxy, methoxy, or CN,

15 CN ,

halo,

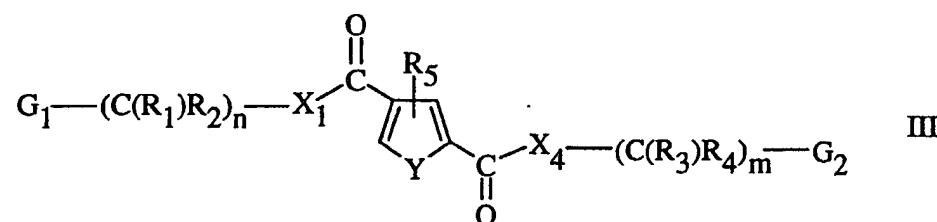
$S(O)-(C_1-C_{12}$ alkyl),

$S(O)_2-(C_1-C_{12}$ alkyl),

20 $S(O)_2-N(R_6)-(R_7)$, wherein R_6 and R_7 are independently hydrogen, C_1-C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above, and

25 $S(O)_2CF_3$; and n and m are independently an integer of from 1 to 3, wherein at least one of R_1 , R_2 , R_3 , R_4 , or R_5 is not hydrogen, or at least one of G_1 or G_2 is substituted C_1-C_{12} alkyl, substituted C_2-C_{12} alkenyl, substituted C_2-C_{12} alkynyl, substituted C_3-C_{12} cycloalkyl, substituted phenyl, substituted naphthyl, or substituted heteroaryl; or

The compound according to Claim 1 of Formula III



45 Y is O, S, or $N-CH_3$;

X_1 and X_4 are each independently O or NH;

G_1 and G_2 are independently selected from:

50 hydrogen,

C_1-C_{12} alkyl,

substituted C_1-C_{12} alkyl,

C_2-C_{12} alkenyl,

substituted C_2-C_{12} alkenyl,

C_2-C_{12} alkynyl,

substituted C_2-C_{12} alkynyl,

C_3-C_{12} cycloalkyl,

substituted C_3-C_{12} cycloalkyl,

phenyl,

substituted phenyl,

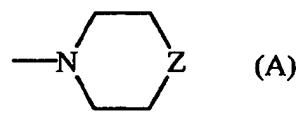
5 naphthyl,
substituted naphthyl,
heteroaryl, and
substituted heteroaryl;

10 R₁, R₂, R₃, and R₄ are independently, at each occurrence, selected from:

15 hydrogen,
methyl,
10 cyano, and
fluoro, or R₁ and R₂, or R₃ and R₄ may be taken together with the carbon atom to which they are each attached to form C=O;

20 R₅ is selected from:

25 hydrogen,
C₁-C₁₂ alkyl,
substituted C₁-C₁₂ alkyl,
C₂-C₁₂ alkenyl,
20 substituted C₂-C₁₂ alkenyl,
C₂-C₁₂ alkynyl,
substituted C₂-C₁₂ alkynyl,
C₃-C₁₂ cycloalkyl,
substituted C₃-C₁₂ cycloalkyl,
25 phenyl,
substituted phenyl,
benzyl,
substituted benzyl,
O-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
30 S-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
C(O)-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
CO₂R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
C(O)-N(H)OH,
35 C(=NOR₆)-H, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
C(=NOR₆)-CH₃, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
CH₂OR₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
40 CH₂N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A)



50 wherein Z is CH₂, O, S, or N-R, wherein R is H or CH₃,

55 C(H)F-OH,
CF₂-OH,
O-C(O)-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
C(O)-N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,
N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated

heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

5 N(R₆)-C(O)-R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,

N(H)-C(O)-N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

10 N(H)-C(O)-OR₆, wherein R₆ is independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,

N(H)-S(O)₂-(C₁-C₁₂ alkyl),

15 O-C(O)-N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

NO₂,

15 N₃,

N(H)-C(NR₈)-N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₄ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above, and R₈ is hydrogen, hydroxy, methoxy, or CN,

20 CN,

halo,

S(O)-(C₁-C₁₂ alkyl),

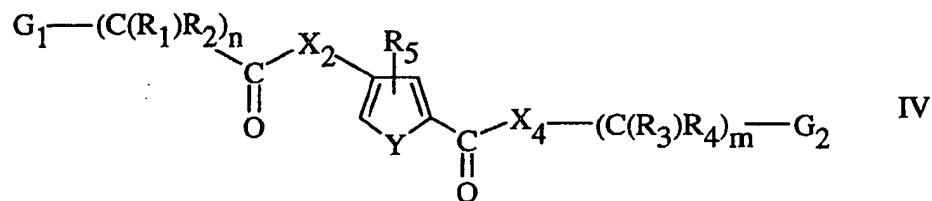
S(O)₂-(C₁-C₁₂ alkyl),

25 S(O)₂-N(R₆)-(R₇), wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above, and

S(O)₂CF₃; and

30 n and m are independently an integer of from 1 to 3, wherein at least one of R₁, R₂, R₃, R₄, or R₅ is not hydrogen, or at least one of G₁ or G₂ is substituted C₁-C₁₂ alkyl, substituted C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkynyl, substituted C₃-C₁₂ cycloalkyl, substituted phenyl, substituted naphthyl, or substituted heteroaryl; or

35 The compound according to Claim 1 of Formula IV



45 or a pharmaceutically acceptable salt thereof;
wherein:

50 Y is O, S, or N-CH₃;

X₂ and X₄ are each independently O or NH;

G₁ and G₂ are independently selected from:

55 hydrogen,

C₁-C₁₂ alkyl,

substituted C₁-C₁₂ alkyl,

C₂-C₁₂ alkenyl,

substituted C₂-C₁₂ alkenyl,

C₂-C₁₂ alkynyl,

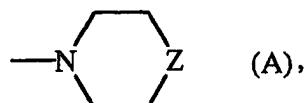
substituted C₂-C₁₂ alkynyl,
 C₃-C₁₂ cycloalkyl,
 substituted C₃-C₁₂ cycloalkyl,
 phenyl,
 substituted phenyl,
 naphthyl,
 substituted naphthyl,
 heteroaryl, and
 substituted heteroaryl;

R_1, R_2, R_3 , and R_4 are independently, at each occurrence, selected from:

hydrogen,
methyl,
cyano, and
fluoro, or R_1 and R_2 , or R_3 and R_4 may be taken together with the carbon atom to which they are each attached to form $C=O$;

R_5 is selected from:

hydrogen,
C₁-C₁₂ alkyl,
substituted C₁-C₁₂ alkyl,
C₂-C₁₂ alkenyl,
substituted C₂-C₁₂ alkenyl,
C₂-C₁₂ alkynyl,
substituted C₂-C₁₂ alkynyl,
C₃-C₁₂ cycloalkyl,
substituted C₃-C₁₂ cycloalkyl,
phenyl,
substituted phenyl,
benzyl,
substituted benzyl,
O-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
S-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
C(O)-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
CO₂R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
C(O)-N(H)OH,
C(=NOR₆)-H, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
C(=NOR₆)-CH₃, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
CH₂OR₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
CH₂N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A)



wherein Z is CH_2 , O, S, or N-R, wherein R is H or CH_3 ,

C(H)F-OH,

CF₂-OH,

O-C(O)-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,

C(O)-N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated

heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

5 $N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

10 $N(R_6)-C(O)-R_7$, wherein R_6 and R_7 are independently hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl,

$N(H)-C(O)-N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

15 $N(H)-C(O)-OR_6$, wherein R_6 is independently hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl,

$N(H)-S(O)_2-(C_1$ - C_{12} alkyl),

20 $O-C(O)-N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

25 NO_2 ,

N_3 ,

20 $N(H)-C(NR_8)-N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1 - C_4 alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above, and R_8 is hydrogen, hydroxy, methoxy, or CN,

25 CN ,

halo,

$S(O)-(C_1$ - C_{12} alkyl),

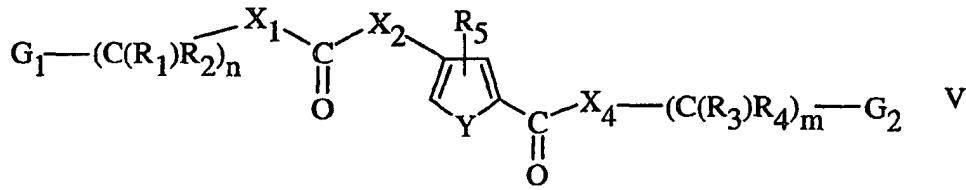
$S(O)_2-(C_1$ - C_{12} alkyl),

30 $S(O)_2-N(R_6)-(R_7)$, wherein R_6 and R_7 are independently hydrogen, C_1 - C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above, and

35 $S(O)_2CF_3$; and

n and m are independently an integer of from 1 to 3, wherein at least one of R_1 , R_2 , R_3 , R_4 , or R_5 is not hydrogen, or at least one of G_1 or G_2 is substituted C_1 - C_{12} alkyl, substituted C_2 - C_{12} alkenyl, substituted C_2 - C_{12} alkynyl, substituted C_3 - C_{12} cycloalkyl, substituted phenyl, substituted naphthyl, or substituted heteroaryl; or

The compound according to Claim 1 of Formula V



50 or a pharmaceutically acceptable salt thereof;

wherein:

55 Y is O, S, or $N-CH_3$;

X_1 , X_2 , and X_4 are each independently O or NH;

G_1 and G_2 are independently selected from:

hydrogen,

C_1 - C_{12} alkyl,

substituted C_1 - C_{12} alkyl,

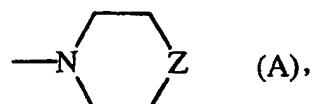
5 C₂-C₁₂ alkenyl,
 substituted C₂-C₁₂ alkenyl,
 C₂-C₁₂ alkynyl,
 substituted C₂-C₁₂ alkynyl,
 C₃-C₁₂ cycloalkyl,
 substituted C₃-C₁₂ cycloalkyl,
 phenyl,
 substituted phenyl,
 naphthyl,
 10 substituted naphthyl,
 heteroaryl, and
 substituted heteroaryl,

15 R₁, R₂, R₃, and R₄ are independently, at each occurrence, selected from:

15 hydrogen,
 methyl,
 cyano, and
 20 fluoro, or R₁ and R₂, or R₃ and R₄ may be taken together with the carbon atom to which they are each attached to form C=O;

25 R₅ is selected from:

25 hydrogen,
 C₁-C₁₂ alkyl,
 substituted C₁-C₁₂ alkyl,
 C₂-C₁₂ alkenyl,
 substituted C₂-C₁₂ alkenyl,
 C₂-C₁₂ alkynyl,
 30 substituted C₂-C₁₂ alkynyl,
 C₃-C₁₂ cycloalkyl,
 substituted C₃-C₁₂ cycloalkyl,
 phenyl,
 substituted phenyl,
 35 benzyl,
 O-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 S-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 C(O)-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 CO₂R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 40 C(O)-N(H)OH,
 C(=NOR₆)-H, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 C(=NOR₆)-CH₃, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 CH₂OR₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
 45 CH₂N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and R₇ are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A)



55 wherein Z is CH₂, O, S, or N-R, wherein R is H or CH₃,
 C(H)F-OH,
 CF₂-OH,
 O-C(O)-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,

5 $\text{C}(\text{O})\text{-N}(\text{R}_6)\text{R}_7$, wherein R_6 and R_7 are independently hydrogen, $\text{C}_1\text{-C}_{12}$ alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

10 $\text{N}(\text{R}_6)\text{R}_7$, wherein R_6 and R_7 are independently hydrogen, $\text{C}_1\text{-C}_{12}$ alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

15 $\text{N}(\text{R}_6)\text{-C}(\text{O})\text{-R}_7$, wherein R_6 and R_7 are independently hydrogen, $\text{C}_1\text{-C}_{12}$ alkyl, phenyl, or benzyl,

20 $\text{N}(\text{H})\text{-C}(\text{O})\text{-N}(\text{R}_6)\text{R}_7$, wherein R_6 and R_7 are independently hydrogen, $\text{C}_1\text{-C}_{12}$ alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

25 $\text{N}(\text{H})\text{-C}(\text{O})\text{-OR}_6$, wherein R_6 is independently hydrogen, $\text{C}_1\text{-C}_{12}$ alkyl, phenyl, or benzyl,

30 $\text{N}(\text{H})\text{-S}(\text{O})_2\text{-}(\text{C}_1\text{-C}_{12}$ alkyl),

35 $\text{O-C}(\text{O})\text{-N}(\text{R}_6)\text{R}_7$, wherein R_6 and R_7 are independently hydrogen, $\text{C}_1\text{-C}_{12}$ alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

40 NO_2 ,

45 N_3 ,

$\text{N}(\text{H})\text{-C}(\text{NR}_8)\text{-N}(\text{R}_6)\text{R}_7$, wherein R_6 and R_7 are independently hydrogen, $\text{C}_1\text{-C}_4$ alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above, and R_8 is hydrogen, hydroxy, methoxy, or CN ,

50 CN ,

halo,

$\text{S}(\text{O})\text{-}(\text{C}_1\text{-C}_{12}$ alkyl),

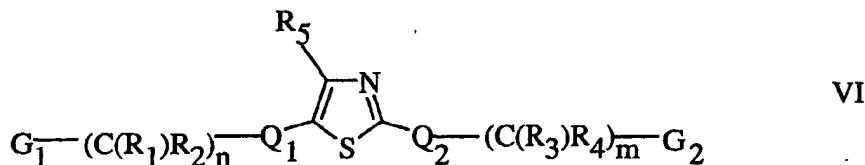
$\text{S}(\text{O})_2\text{-}(\text{C}_1\text{-C}_{12}$ alkyl),

55 $\text{S}(\text{O})_2\text{-N}(\text{R}_6)\text{-}(\text{R}_7)$, wherein R_6 and R_7 are independently hydrogen, $\text{C}_1\text{-C}_{12}$ alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above, and

$\text{S}(\text{O})_2\text{CF}_3$; and

60 n and m are independently an integer of from 1 to 3, wherein at least one of R_1 , R_2 , R_3 , R_4 , or R_5 is not hydrogen, or at least one of G_1 or G_2 is substituted $\text{C}_1\text{-C}_{12}$ alkyl, substituted $\text{C}_2\text{-C}_{12}$ alkenyl, substituted $\text{C}_2\text{-C}_{12}$ alkynyl, substituted $\text{C}_3\text{-C}_{12}$ cycloalkyl, substituted phenyl, substituted naphthyl, or substituted heteroaryl; or

65 The compound according to Claim 1 of Formula VI

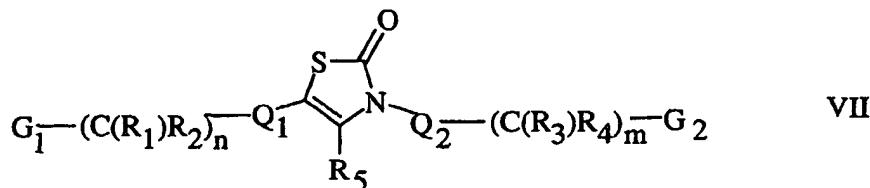


80 or a pharmaceutically acceptable salt thereof, wherein G_1 , G_2 , R_1 , R_2 , R_3 , R_4 , R_5 , n , m , Q_1 , and Q_2 are as defined above for Formula I in Claim 1; or

85 The compound according to Claim 1 of Formula VII

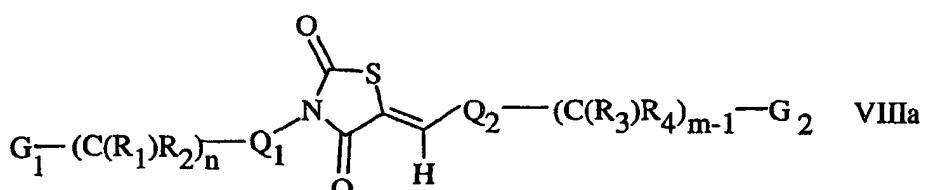
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10 or a pharmaceutically acceptable salt thereof, wherein G_1 , G_2 , R_1 , R_2 , R_3 , R_4 , R_5 , n , m , Q_1 , and Q_2 are as defined above for Formula I in Claim 1; or
 The compound according to Claim 1 of Formula VIIa

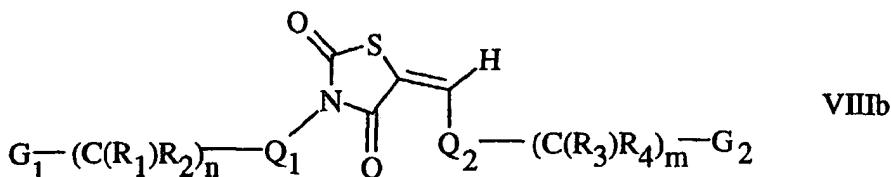
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20

or a pharmaceutically acceptable salt thereof, or a compound of Formula VIIb

25



30

35 or a pharmaceutically acceptable salt thereof, wherein G_1 , G_2 , R_1 , R_2 , R_3 , R_4 , n , m , Q_1 , and Q_2 are as defined above for Formula I in Claim 1.

3. The compound according to Claim 2 of Formula II, or a pharmaceutically acceptable salt thereof, selected from:

40 thiophene-2,5-dicarboxylic acid, bis[(1,3-benzodioxol-5-ylmethyl) ester];
 thiophene-2,5-dicarboxylic acid, bis[(1,3-benzodioxol-5-ylmethyl) amide];
 thiophene-2,5-dicarboxylic acid, 3-methoxy-, bis[(1,3-benzodioxol-5-ylmethyl) ester]; and
 thiophene-2,5-dicarboxylic acid, 3-methoxy-, bis[(1,3-benzodioxol-5-ylmethyl) amide]; or

45 The compound according to Claim 2 of Formula III, or a pharmaceutically acceptable salt thereof, selected from:

thiophene-2,4-dicarboxylic acid, bis[(1,3-benzodioxol-5-ylmethyl) ester];
 thiophene-2,4-dicarboxylic acid, bis[(1,3-benzodioxol-5-ylmethyl) amide];
 1*H*-pyrrole-2,4-dicarboxylic acid, 1-methyl-, bis[(1,3-benzodioxol-5-ylmethyl) ester]; and
 1*H*-pyrrole-2,4-dicarboxylic acid, 1-methyl-, bis[(1,3-benzodioxol-5-ylmethyl) amide]; or

The compound according to Claim 2 of Formula IV, or a pharmaceutically acceptable salt thereof, selected from:

55 thiophene-2-carboxylic acid, 5-methyl-4-phenylacetylamo-, benzyl ester;
 thiophene-2-carboxylic acid, 5-methyl-4-phenylacetylamo-, benzyl amide;
 thiophene-2-carboxylic acid, 5-methyl-4-phenylacetylamo-, 1,3-benzodioxol-5-ylmethyl ester; and
 thiophene-2-carboxylic acid, 5-methyl-4-phenylacetylamo-, 1,3-benzodioxol-5-ylmethyl amide; or

The compound according to Claim 2 of Formula V, or a pharmaceutically acceptable salt thereof, selected from:

5 thiophene-2-carboxylic acid, 4-(3-benzyl-ureido)-5-methyl-, methyl ester;
 thiophene-2-carboxylic acid, 4-(3-benzyl-ureido)-5-methyl-, methyl amide;
 thiophene-2-carboxylic acid, 4-(3-benzyl-ureido)-5-methyl-, benzyl ester;
 thiophene-2-carboxylic acid, 4-(3-benzyl-ureido)-5-methyl-, benzyl amide;
 thiophene-2-carboxylic acid, 4-(3-benzyl-ureido)-5-methyl-, (1,3-benzodioxol-5-ylmethyl) ester; and
 thiophene-2-carboxylic acid, 4-(3-benzyl-ureido)-5-methyl-, (1,3-benzodioxol-5-ylmethyl) amide; or

10 The compound according to Claim 2 of Formula VI, or a pharmaceutically acceptable salt thereof, which is 3-methoxy-cyclopentylmethylcarboxylic acid 5-(2-naphthalen-2-yl-ethylcarbamoyl)-4-phenyl-thiazol-2-yl ester; or
 The compound according to Claim 2 of Formula VII, or a pharmaceutically acceptable salt thereof, which is [2-(1H-indol-3-yl)-2-oxo-ethyl]-carbamic acid 3-(3-methyl-but-2-enylcarbamoyl)-2-oxo-2,3-dihydro-thiazol-5-yl ester; or
 The compound according to Claim 2 of Formula VIIa or VIIb which is (*Z*)-5-(2,2-difluoro-hex-5-ynoyloxymethylene)-2,4-dioxo-thiazolidine-3-carboxylic acid 5-chloro-thiophen-2-ylmethyl ester or (*E*)-5-(2,2-difluorohex-5-ynoyloxymethylene)-2,4-dioxo-thiazolidine-3-carboxylic acid 5-chloro-thiophen-2-ylmethyl ester.

15 4. A pharmaceutical composition, comprising a compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable carrier, excipient, or diluent.

20 5. The use of a compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting MMP-13.

25 6. The use of a compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease mediated by MMP-13 enzymes and optionally from 0 to 15 additional MMP enzymes.

30 7. The use according to Claim 6, wherein the disease is selected from: an autoimmune disease, a hyper-immune disease, cancer, inflammation, heart failure, rheumatoid arthritis, osteoarthritis, asthma, osteoporosis, periodontitis, gingivitis, multiple sclerosis, corneal epidermal ulceration, gastric ulceration, stroke, renal disease, macular degeneration, atherosclerosis, neointimal proliferation, and cancer metastasis.

35 8. The use of a compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for preventing connective tissue or extracellular matrix degradation mediated by MMP-13 and optionally from 0 to 15 additional MMP enzymes.

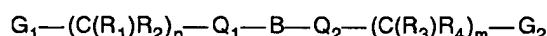
40 9. The use according to Claim 8, wherein the patient being treated is at risk for, or has a disease selected from cancer, inflammation, heart failure, asthma, cancer metastasis, multiple sclerosis, corneal epidermal ulceration, gastric ulceration, stroke, renal disease, macular degeneration, atherosclerosis, neointimal proliferation, osteoporosis, periodontitis, gingivitis, an autoimmune disease, a hyper-immune disease, and arthritis, including osteoarthritis and rheumatoid arthritis.

45 10. A compound according to any one of claims 1 to 3 for use in medicine.

50 11. A compound according to any one of claims 1 to 3 for use in the treatment of a disease selected from: an autoimmune disease, a hyper-immune disease, cancer, inflammation, heart failure, rheumatoid arthritis, osteoarthritis, asthma, osteoporosis, periodontitis, gingivitis, multiple sclerosis, corneal epidermal ulceration, gastric ulceration, stroke, renal disease, macular degeneration, atherosclerosis, neointimal proliferation, and cancer metastasis.

55 12. A pharmaceutical composition, comprising a means for inhibiting MMP-13 and a pharmaceutically acceptable carrier, diluent, or excipient.

60 13. An inhibitor of MMP-13, comprising an inhibitor of MMP-13 of Formula I



1

or a pharmaceutically acceptable salt thereof,
wherein:

5 G_1 and G_2 are independently selected from:

hydrogen,
C₁-C₁₂ alkyl,
substituted C₁-C₁₂ alkyl,
C₂-C₁₂ alkenyl,
10 substituted C₂-C₁₂ alkenyl,
C₂-C₁₂ alkynyl,
substituted C₂-C₁₂ alkynyl,
C₃-C₁₂ cycloalkyl,
15 substituted C₃-C₁₂ cycloalkyl,
phenyl,
substituted phenyl,
naphthyl,
substituted naphthyl,
heteroaryl, and
20 substituted heteroaryl;

R₁, R₂, R₃, and R₄ are independently, at each occurrence, selected from:

25 hydrogen,
methyl,
cyano, and
fluoro, or R₁ and R₂, or R₃ and R₄, may be taken together with the carbon atom to which they are each attached to form C=O;

30 n and m are independently an integer of from 1 to 3;

Q₁ is



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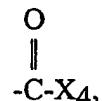
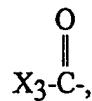
$$\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{X}_2, \end{array}$$

45 , or

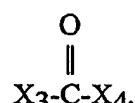


55 wherein X₁ and X₂ are independently O or N(H);

Q₂ is



or

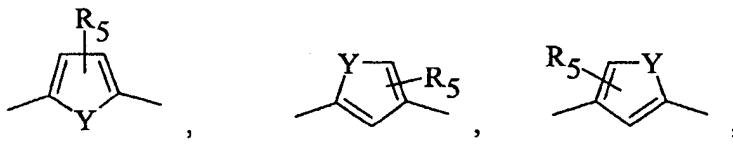


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wherein X_3 and X_4 are independently O or N(H); and

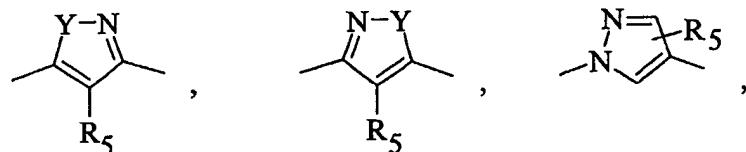
B is a 5-membered heterocyclene selected from:

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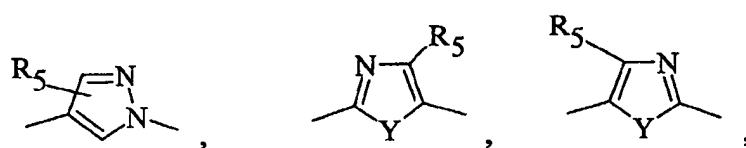
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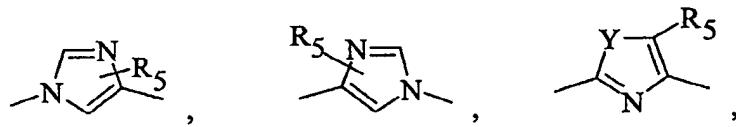


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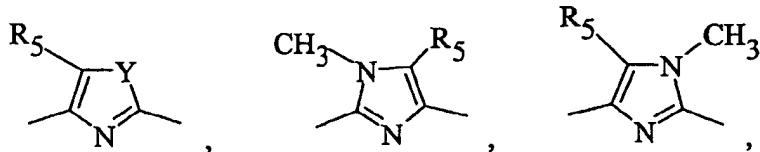


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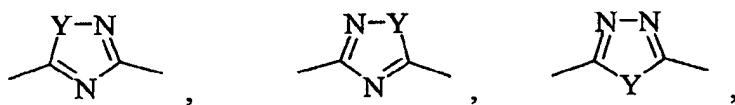


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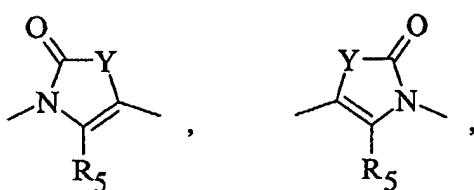


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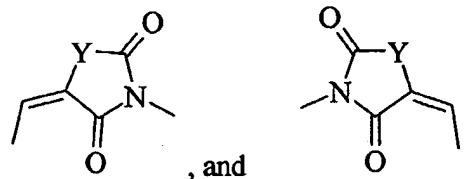
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wherein Y is O, S, or N-CH₃, and

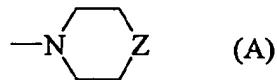
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R₅ is selected from:

- hydrogen,
- C₁-C₁₂ alkyl,
- substituted C₁-C₁₂ alkyl,
- 40 C₂-C₁₂ alkenyl,
- substituted C₂-C₁₂ alkenyl,
- C₂-C₁₂ alkynyl,
- substituted C₂-C₁₂ alkynyl,
- 45 C₃-C₁₂ cycloalkyl,
- substituted C₃-C₁₂ cycloalkyl,
- phenyl,
- substituted phenyl,
- benzyl,
- substituted benzyl,
- 50 O-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
- S-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
- C(O)-R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
- CO₂R₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
- C(O)-N(H)OR₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
- 55 C(=NOR₆)-H, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
- C(=NOR₆)-CH₃, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
- CH₂OR₆, wherein R₆ is hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl,
- CH₂N(R₆)R₇, wherein R₆ and R₇ are independently hydrogen, C₁-C₁₂ alkyl, phenyl, or benzyl, or R₆ and

R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A)

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wherein Z is CH_2 , O, S, or $N-R$, wherein R is H or CH_3 ,

$C(H)F-OH$,

CF_2-OH ,

$O-C(O)-R_6$, wherein R_6 is hydrogen, C_1-C_{12} alkyl, phenyl, or benzyl,

15

$C(O)-N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1-C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

20

$N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1-C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

$N(R_6)-C(O)-R_7$, wherein R_6 and R_7 are independently hydrogen, C_1-C_{12} alkyl, phenyl, or benzyl,

25

$N(H)-C(O)-N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1-C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

$N(H)-C(O)-OR_6$, wherein R_6 is independently hydrogen, C_1-C_{12} alkyl, phenyl, or benzyl,

30

$N(H)-S(O)_2(C_1-C_{12}$ alkyl),

$O-C(O)-N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1-C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above,

NO_2 ,

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N_3 ,

$N(H)-C(NR_8)-N(R_6)R_7$, wherein R_6 and R_7 are independently hydrogen, C_1-C_4 alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above, and R_8 is hydrogen, hydroxy, methoxy, or CN ,

40

CN ,

halo,

$S(O)-(C_1-C_{12}$ alkyl),

$S(O)_2(C_1-C_{12}$ alkyl),

45

$S(O)_2-N(R_6)-(R_7)$, wherein R_6 and R_7 are independently hydrogen, C_1-C_{12} alkyl, phenyl, or benzyl, or R_6 and R_7 are taken together with the nitrogen atom to which they are attached to form a 5-membered, saturated heterocyclic ring having 1 nitrogen atom and 4 carbon atoms or a 6-membered, saturated heterocyclic ring of formula (A), wherein (A) is as defined above, and

50

$S(O)_2CF_3$, wherein at least one of R_1 , R_2 , R_3 , R_4 , or R_5 is not hydrogen, or at least one of G_1 or G_2 is substituted C_1-C_{12} alkyl, substituted C_2-C_{12} alkenyl, substituted C_2-C_{12} alkynyl, substituted C_3-C_{12} cycloalkyl, substituted phenyl, substituted naphthyl, or substituted heteroaryl.

55

14. The compound according to Claim 2 of Formula II, named 3-methoxythiophene-2,5-dicarboxylic acid bis benzylamide, or a pharmaceutically acceptable salt thereof.

15. The compound according to Claim 2 of Formula III, named 4-({[5-(4-methoxy-benzylcarbamoyl)-2-methylamino-thiophene-3-carbonyl]-amino}-methyl)-2-methyl-benzoic acid, or a pharmaceutically acceptable salt thereof.

16. The compound according to Claim 1, named 5-(3-benzyl-ureido)-1,3,4-thiadiazole-2-carboxylic acid benzyl ester, or a pharmaceutically acceptable salt thereof.

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PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 02 25 5922
shall be considered, for the purposes of subsequent
proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	US 6 232 338 B1 (DAVIES ET. AL.) 15 May 2001 (2001-05-15) * claims; example 12 * ---	1,4	C07D333/70 C07D409/14 C07D409/12 C07D417/12
X	EP 0 387 725 A (SUMITOMO) 19 September 1990 (1990-09-19) * claims; examples 5-7,11 * ---	1	C07D277/56 C07D277/34 A61K31/381 A61K31/404
X	M. W. ROOMI ET. AL. : "The Hantzsch Pyrrole Synthesis" CANADIAN JOURNAL OF CHEMISTRY, vol. 48, 1970, pages 1689-97, XP009003599 * table 2 * ---	1	A61K31/425 A61K31/426 A61P35/00
X	WO 00 00486 A (BIOCHEM PHARMA) 6 January 2000 (2000-01-06) * page 6, line 20 - line 32; claims; examples * ---	1,4	
A	WO 01 62750 A (ASTRAZENECA) 30 August 2001 (2001-08-30) * page 2, line 22 - page 4, line 27; claims; examples * ---	1-16 -/-	TECHNICAL FIELDS SEARCHED (Int.Cl.7) C07D
INCOMPLETE SEARCH			
The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.			
Claims searched completely:			
3			
Claims searched incompletely:			
1,2,4-16			
Claims not searched:			
Reason for the limitation of the search:			
Due to the very broad scope of the general formulae (I)-(VIII) a complete search cannot be carried out within a reasonable time limit. The search has been carried out on the basis of the prepared examples (see Guidelines, B-III, 3.7).			
Place of search	Date of completion of the search	Examiner	
MUNICH	9 January 2003	Helps, J	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			



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PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 25 5922

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
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